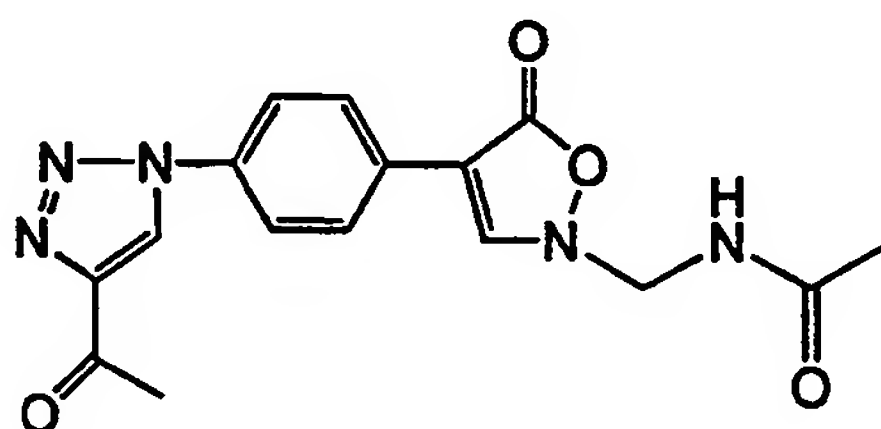


**EXAMPLE 18****N-({4-[4-(4-acetyl(1,2,3-triazolyl))phenyl]-5-oxo-2-hydroisoxazol-2-yl}methyl)acetamide**

5

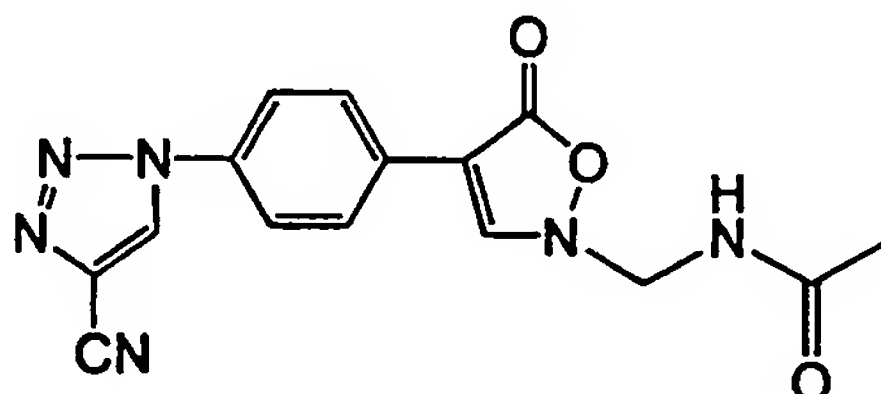


A mixture of N-{{4-[4-(4-azidophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (100 mg, 0.36 mmol) and of 3-butyne-2-one (0.035 mL, 0.72 mmol) in 3 mL DMF was heated at 50°C for 24 hours. The reaction mixture was concentrated in vacuo and then triturated with EtOAc to yield 60 mg (49%) of the title compound as a yellow solid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 9.47 (s, 1 H), 9.35, (s, 1 H), 8.98, (t, J = 6 Hz, 1 H), 8.02 (s, 4 H), 5.08 (d, J = 6 Hz, 2 H), 3.32 (s, 3 H), 1.85 (s, 3 H).

15

**EXAMPLE 19****N-({4-[4-(4-cyano(1,2,3-triazolyl))phenyl]-5-oxo-2-hydroisoxazol-2-yl}methyl)acetamide**

20



A mixture of N-{{4-[4-(4-azidophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (500 mg, 1.83 mmol) and 0.8 mL of cyanoacetylene

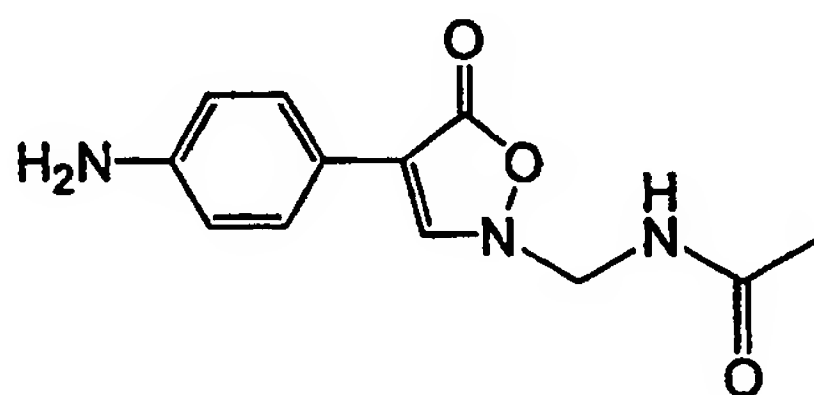
25

[prepared according to Murahashi, S.; Takizawa, T.; Kurioka, S.; Maekawa, S.; in J. Chem. Soc. Jap., 77, p, 1689, 1956] in 5 mL of DMF was heated at 50°C for 48 hours. Upon cooling, the precipitated solid was collected by filtration and washed with DMF to yield 375 mg (63%) of the title compound as a white solid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 9.75 (s, 1 H), 9.17, (s, 1 H), 9.00, (t, *J* = 6 Hz, 1 H), 8.05 (d, *J* = 9 Hz, 2 H), 7.95 (d, *J* = 9 Hz, 2 H), 5.10 (d, *J* = 6 Hz, 2 H), 1.85 (s, 3 H).

### EXAMPLE 20

10

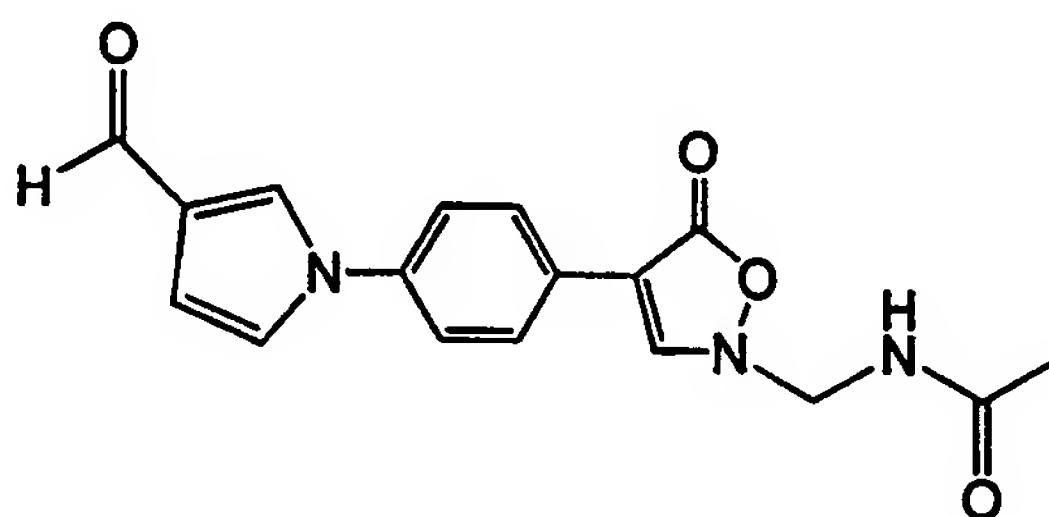
#### N-{[4-(4-aminophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide



15 To a mixture of N-{[4-(4-azidophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (3 g, 10.98 mmol) in 40 mL EtOAc and 20 mL MeOH was added SnCl<sub>2</sub>•2H<sub>2</sub>O (12.5 g, 54.9 mmol). After all of the solid was dissolved, the reaction mixture was concentrated in vacuo and neutralized with saturated aqueous sodium bicarbonate. The mixture was  
20 concentrated in vacuo again and the residue was dissolved in a mixture of 4:1 CHCl<sub>3</sub>/MeOH. The resulting solution was filtered through celite, and the insoluble material was discarded. The filtrate was then concentrated in vacuo to yield 3 g (100%) of the title compound as a yellow solid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.83, (t, *J* = 6 Hz, 1 H), 8.55, (s, 1 H), 7.43 (d, *J* = 9 Hz, 2 H), 6.56 (d, *J* = 9 Hz, 2 H), 5.21, (broad s, 2 H), 4.91 (d, *J* = 6 Hz, 2 H), 1.82 (s, 3 H).

**EXAMPLE 21****N-([4-[4-(3-formylpyrrolyl)phenyl]-5-oxo-2-hydroisoxazol-2-yl]methyl)acetamide**

5

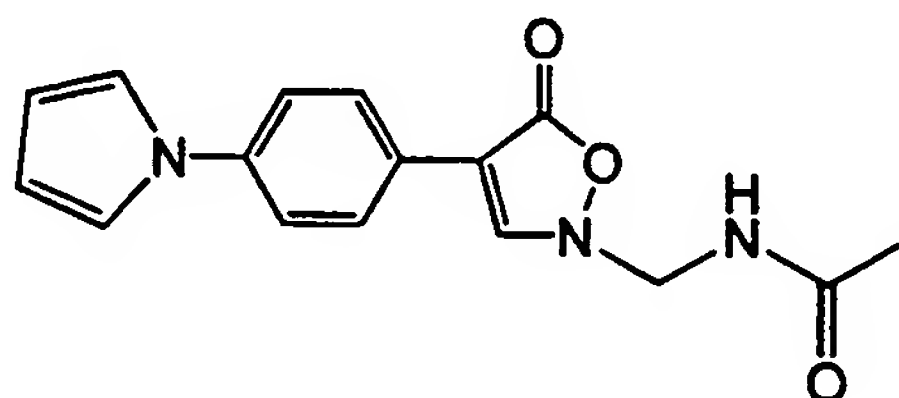


To a solution of N-([4-(4-aminophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl)acetamide (200 mg, 0.81 mmol) in 3 mL of acetic acid was added 2,5-dimethoxy-3-tetrahydrofurancarboaldehyde (184 mg, 1.27 mmol). This mixture was refluxed for 0.5 hours, and then concentrated in vacuo to give the crude product. Purification by silica gel chromatography (eluting with EtOAc, then 8% MeOH in EtOAc) gave 240 mg (91%) of the title compound as a yellow solid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 9.79 (s, 1 H), 9.08, (s, 1 H), 9.00, (t, J = 6 Hz, 1 H), 8.29, (m, 1 H), 7.93 (d, J = 9 Hz, 2 H), 7.74 (d, J = 9 Hz, 2 H), 7.58, (m, 1 H), 6.71 (m, 1 H), 5.06 (d, J = 6 Hz, 2 H), 1.86 (s, 3 H).

15

**EXAMPLE 22**

20

**N-([5-oxo-4-(4-pyrrolyl)phenyl]-2-hydroisoxazol-2-yl]methyl)acetamide**

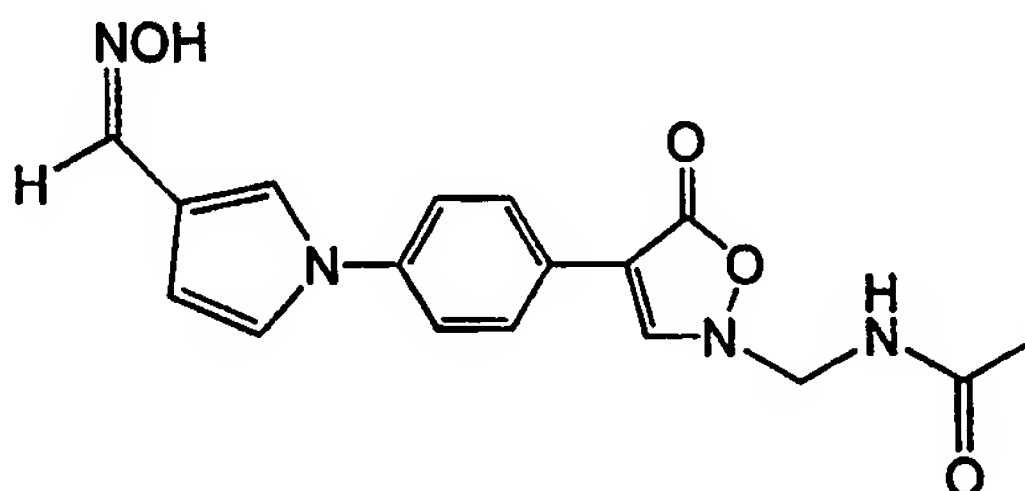
This compound was prepared from N-([4-(4-aminophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl)acetamide as described above for N-([4-[4-(3-formylpyrrolyl)phenyl]-5-oxo-2-hydroisoxazol-2-yl]methyl)acetamide  
5 except that 2,5-dimethoxy-3-tetrahydrofuran was used in place of 2,5-dimethoxy-3-tetrahydrofurancarboaldehyde. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.92, (s, 1 H), 8.94, (t, J = 6 Hz, 1 H), 7.85 (d, J = 9 Hz, 2 H), 7.62 (d, J = 9 Hz, 2 H), 7.40, (t, J = 2 Hz, 2 H), 6.27 (t, J = 2 Hz, 2 H), 5.04 (d, J = 6 Hz, 2 H), 1.86 (s, 3 H).

10

### EXAMPLE 23

N-([4-[4-[3-((hydroxyimino)methyl)pyrrolyl]phenyl]-5-oxo-2-hydroisoxazol-2-yl]methyl]acetamide

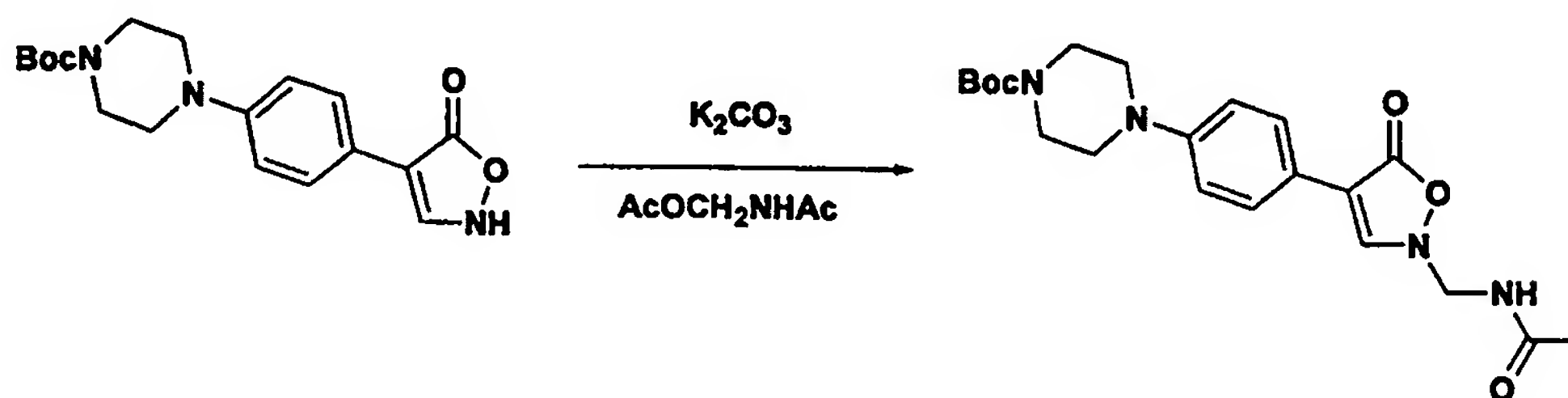
15



A mixture of N-([4-[4-(3-formylpyrrolyl)phenyl]-5-oxo-2-hydroisoxazol-2-yl]methyl)acetamide (100 mg, 0.30 mmol) and 50%  
20 aqueous NH<sub>2</sub>OH (40 mg, 0.60 mmol) in 3 mL of MeOH was heated at reflux for 2 hours. The reaction mixture was then concentrated in vacuo and the residue was triturated with ether to yield 96 mg (94%) of the title compound as a yellow solid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.6 (s, 1 H), 9.02, (s, 1 H), 8.95, (t, J = 6 Hz, 1 H), 8.00, (s, 1 H), 7.87 (d, J = 9 Hz, 2 H), 7.66, (s, 1 H), 7.63 (d, J = 9 Hz, 2 H), 7.45, (m, 1 H), 6.50 (m, 1 H),  
25 5.04 (d, J = 6 Hz, 2 H), 1.85 (s, 3 H).

**EXAMPLE 24****t-Butyl 4-(4-{2-[(acetylamino)methyl]-5-oxo-2-hydroisoxazol-4-yl}phenyl)piperazine carboxylate**

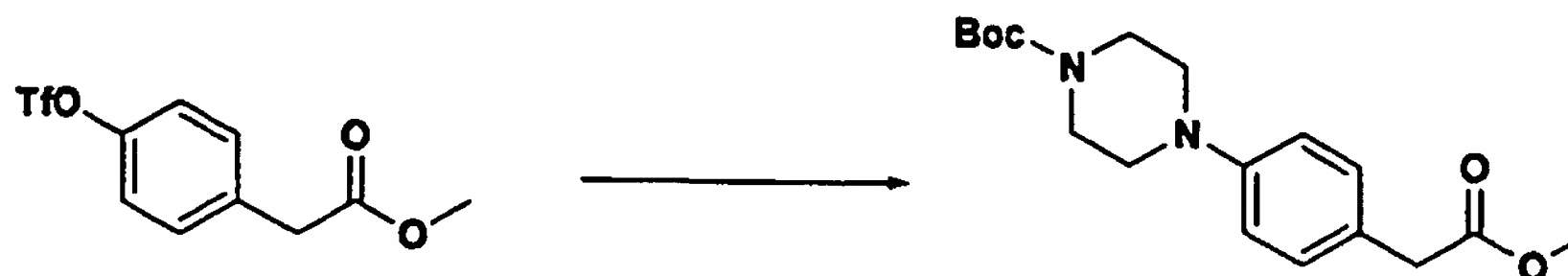
5



To t-butyl 4-[4-(5-oxo-2-hydroisoxazol-4-yl)phenyl]piperazinecarboxylate (1.5 g, 4.3 mmol) in 35 mL dimethylformamide was added N-(hydroxymethyl)acetamide acetate (2.9 g, 22.0 mmol) followed by potassium carbonate (3.0 g, 22.0 mmol). After 5 hours the reaction mixture was poured into ice water. After 18 hours the precipitate was filtered and dried in vacuo to provide 1.4 g (77%) of the title compound. <sup>1</sup>H NMR (methanol-d<sub>4</sub>; 300 MHz) δ 8.48 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.07 (s, 2H), 3.58 (t, *J* = 4.8 Hz, 4H), 3.17 (t, *J* = 5.2 Hz, 4H), 1.94 (s, 3H), 1.50 (s, 9H); ESI (M+H)<sup>+</sup> = 417.

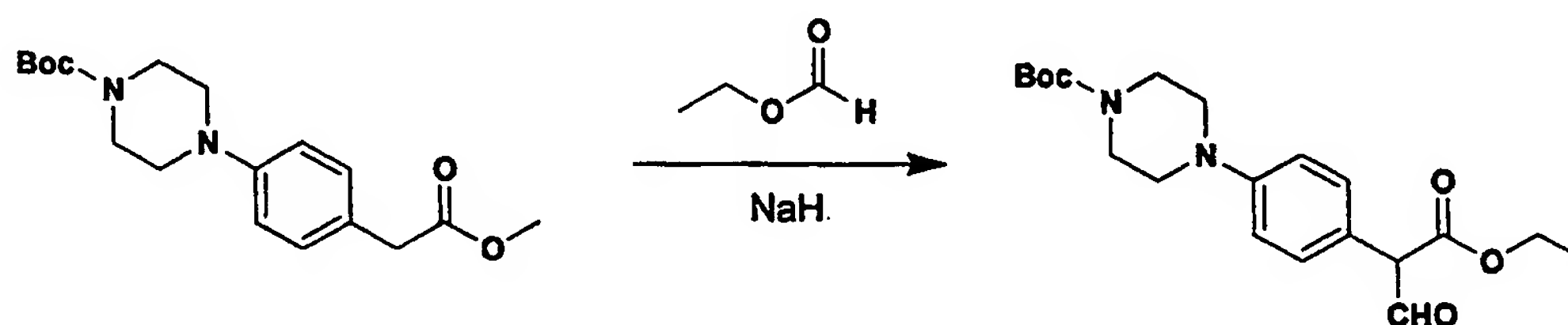
The starting materials were prepared as follows:

20

**Methyl 2-(4-{4-[(t-butyl)oxycarbonyl]piperazinyl}phenyl) acetate**

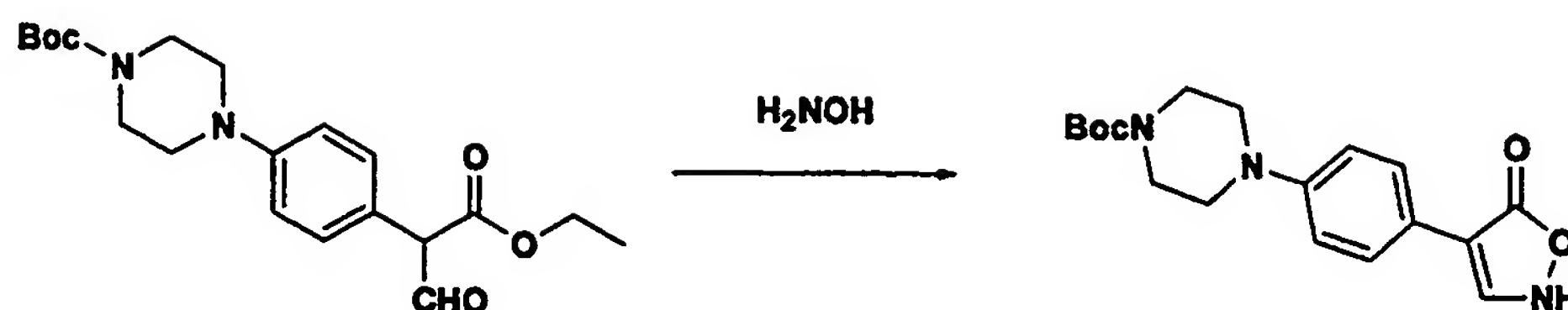
A flask charged with cesium carbonate (4.6 g, 14.0 mmol), palladium (II) acetate (0.07 g, 0.3 mmol), and (S)-BINAP (0.28 g, 4.5mmol) was evacuated and flushed with dry nitrogen. Methyl 2-{4-  
 5 [(trifluoromethyl)sulfonyloxy]phenyl} acetate (3.0 g, 10.0 mmol) and t-butyl-1-piperazinecarboxylate (2.3 g, 12.0 mmol) in 20 mL toluene was added via syringe and the resultant mixture was stirred at ambient temperature for 30 minutes and at 80°C for 16 hours. The reaction mixture was removed from the heating bath, concentrated, and chromatographed on silica gel (0 to 30% ethyl acetate / hexane) providing  
 10 1.7 g (50%) of the title compound. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.20 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 3.70 (s, 3H), 3.59 (t, *J* = 5.0 Hz, 4H), 3.57 (s, 2H), 3.12 (t, *J* = 5.2 Hz, 4H), 1.50 (s, 9H); ESI (M+H)<sup>+</sup> = 335.

15 Ethyl 2-(4-{4-[(t-butyl)oxycarbonyl]piperazinyl})phenyl)-3-oxopropanoate



To methyl 2-(4-{4-[(t-butyl)oxycarbonyl]piperazinyl})phenyl) acetate  
 20 (0.67 g, 2.0 mmol) in 8 mL ethyl formate was added sodium hydride (60% dispersion in mineral oil) (0.32 g, 8.0 mmol) portionwise. After 1.5 hours, the reaction mixture was poured into saturated sodium bicarbonate, and extracted three times with ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and  
 25 concentrated. The crude product was used directly in the next step without further purification.

t-Butyl 4-[4-(5-oxo-2-hydroisoxazol-4-yl)phenyl]piperazinecarboxylate

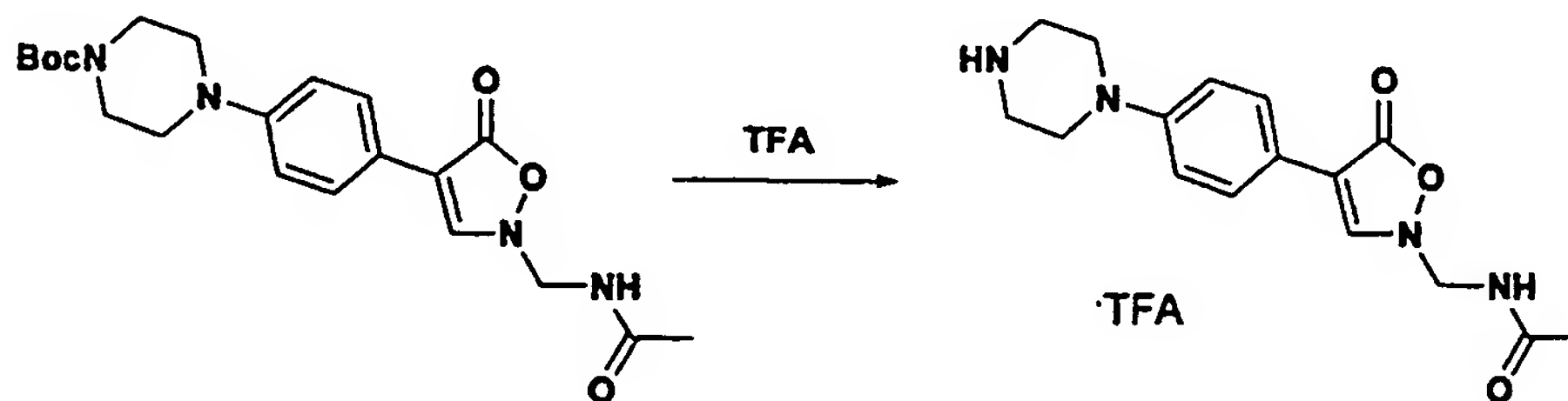


To ethyl 2-(4-(4-((t-butyl)oxycarbonyl)piperazinyl))phenyl)-3-oxopropanoate (7.8 g, 20.7 mmol) in 140 mL methanol and 40 mL water was added hydroxylamine (50% in water, 3.0 mL, 49.0 mmol). The reaction mixture was heated to reflux for 3 hours, cooled and concentrated. The residue was triturated with water and the precipitate was filtered, dried and washed with ether to provide 4.3 g of the title compound. The aqueous solution was lyophilized providing an additional 1.5 g of the title compound. <sup>1</sup>H NMR (methanol-d<sub>4</sub>; 300 MHz) δ 8.35 (s, 1H), 7.58 (br d, J = , 2H), 6.96 (d, J = 8.2 Hz, 2H), 3.58 (t, J = 4.6 Hz, 4H), 3.10 (br s, 4H), 1.50 (s, 9H); ESI (M+H)<sup>+</sup> = 345.

15

**EXAMPLE 25**

**N-[[5-oxo-4-(piperazinylphenyl)-2-hydroisoxazol-2-yl]methyl]acetamide trifluoroacetate salt**



20

To t-butyl 4-(4-{2-[(acetylamino)methyl]-5-oxo-2-hydroisoxazol-4-yl}phenyl)piperazine carboxylate (0.3 g, 0.7 mmol) in 5 mL dichloromethane was added 2 mL trifluoroacetic acid. After 30 minutes, the reaction mixture was concentrated and triturated with ether to provide

25

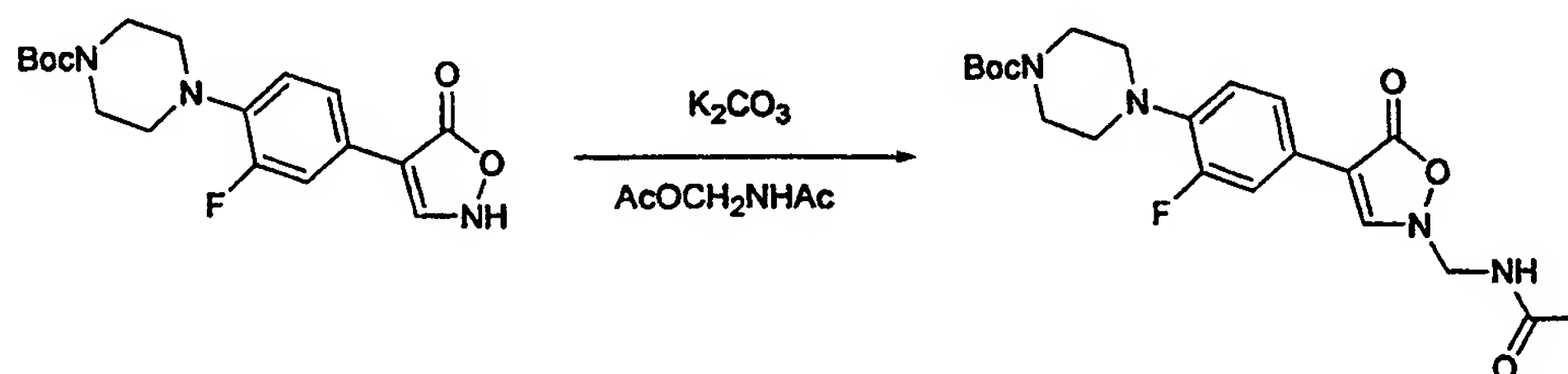
0.3 g (97%) of the title compound.  $^1\text{H}$  NMR (methanol- $d_4$ ; 300 MHz)  $\delta$  9.00 (t,  $J = 6.0$  Hz, 1H), 8.23 (s, 1H), 7.70 (d,  $J = 8.8$  Hz, 2H), 7.05 (d,  $J = 8.7$  Hz, 2H), 5.08 (d,  $J = 6.2$  Hz, 2H), 3.45-3.38 (m, 8H), 1.95 (s, 3H); ESI  $(\text{M}+\text{H})^+ = 317$ .

5

### EXAMPLE 26

#### tert-Butyl 4-(4-{2-[(acetylamino)methyl]-5-oxo(2-hydroisoxazol-4-yl)}-2-fluorophenyl)piperazinecarboxylate

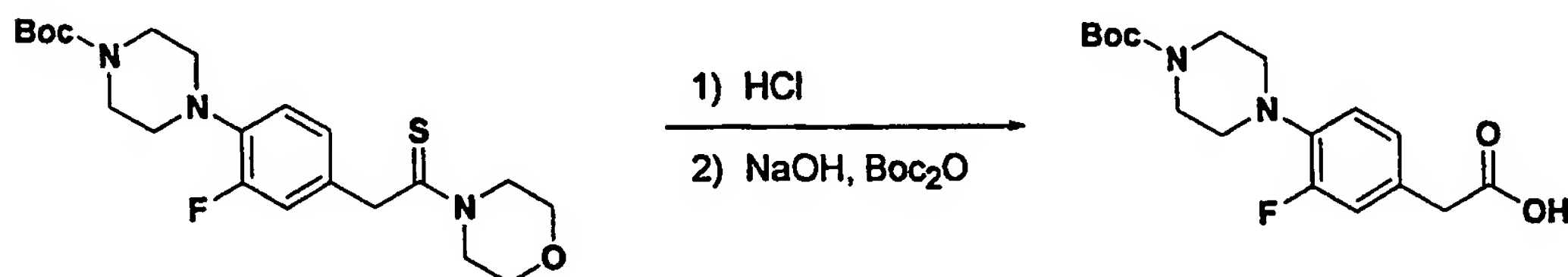
10



Prepared according to the general procedures outlined in Schemes 1, 3, and 6. The starting materials were prepared as follows:

15

#### 2-(4-{4-[(t-butyl)oxycarbonyl]piperazinyl}-3-fluorophenyl)acetic acid



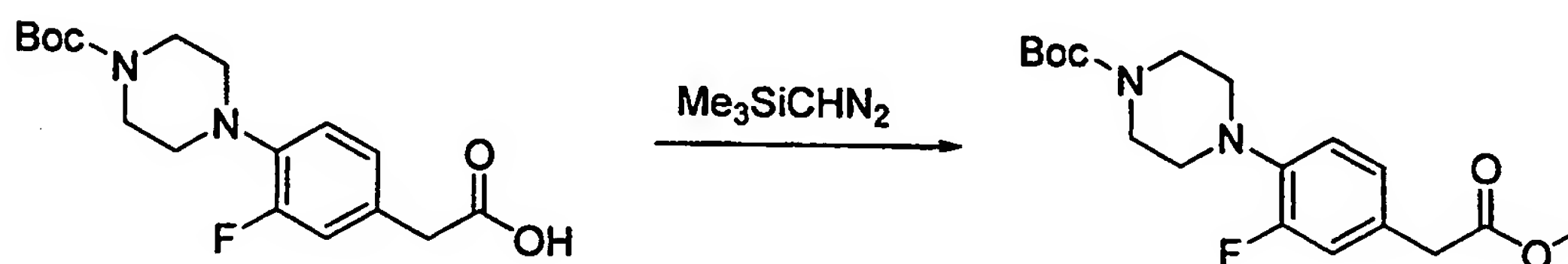
20

To t-butyl 4-[2-fluoro-4-(2-morpholin-4-yl-2-thioxoethyl)phenyl]piperazinecarboxylate (4.2 g, 10 mmol) was added 22 mL of concentrated hydrochloric acid at  $0^\circ\text{C}$ . The resulting mixture was heated to reflux for 1.5 hours, cooled to  $0^\circ\text{C}$ , and 23 mL of 10N sodium hydroxide was added to bring the pH to 14. Then 50 mL water was

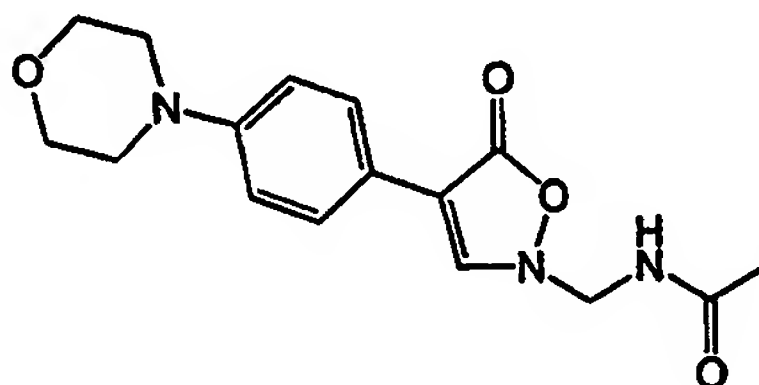


added followed by di-*t*-butyl dicarbonate (5.6 g, 26.0 mmol) in 5 mL tetrahydrofuran. The resulting mixture was allowed to stir at 0°C for 30 minutes and then for 1 hour at ambient temperature at which time it was diluted with 200 mL water. Then 5 mL sodium hydroxide was added to  
5 adjust the pH to 14, and the reaction mixture was extracted with ether. The aqueous layer was acidified to pH 3 by the careful addition of 6N hydrochloric acid and then extracted with three portions of ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The resultant residue was dissolved in  
10 dichloromethane and hexanes were added to produce a precipitate which was collected by filtration providing 3.0 g (89%) of the title product. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 300 MHz) δ 7.04-6.98 (m, 2H), 6.90 (t, *J* = 8.3 Hz, 1H), 3.60 (m, 6H), 3.02 (t, *J* = 5.0 Hz, 4H), 1.50 (s, 3H); ESI (M+H)<sup>+</sup>=339.

15 Methyl 2-(4-{4-[(*t*-butyl)oxycarbonyl]piperazinyl}-3-fluorophenyl)acetate

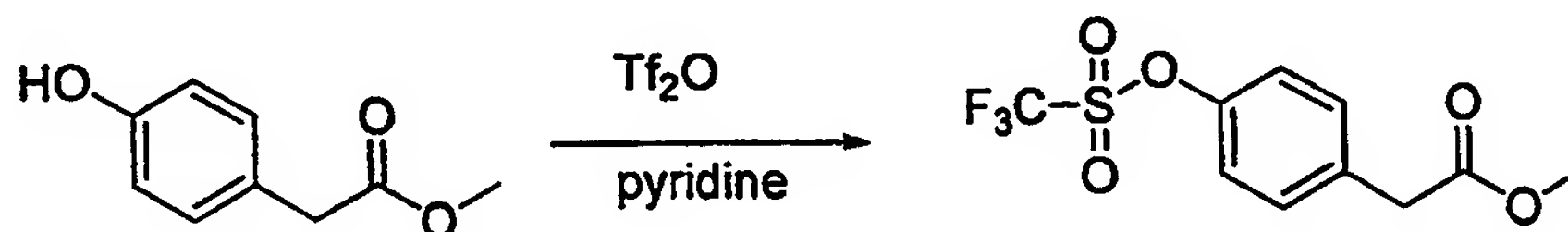


To 2-(4-{4-[(*t*-butyl)oxycarbonyl]piperazinyl}-3-fluorophenyl)acetic  
20 acid (0.3 g, 1.0 mmol) in 2 mL methanol and 7 mL benzene was added trimethylsilyldiazomethane (0.65 mL, 1.30 mmol). After stirring at ambient temperature for 1 hour, the reaction mixture was concentrated to provide 0.36 g (99%) of the title compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 300 MHz) δ 7.00 (m, 2H), 6.90 (t, *J* = 8.3 Hz, 1H), 3.71 (s, 3H), 3.61 (t, *J* = 4.9 Hz, 4H), 3.57 (s, 2H), 3.02 (t, *J* = 5.0 Hz, 4H), 1.50 (s, 9H); ESI (M+H)<sup>+</sup> = 353.  
25

**EXAMPLE 27****N-[[4-(4-morpholinylphenyl)-5-oxo-2-isoxazoliny]methyl]acetamide**

5

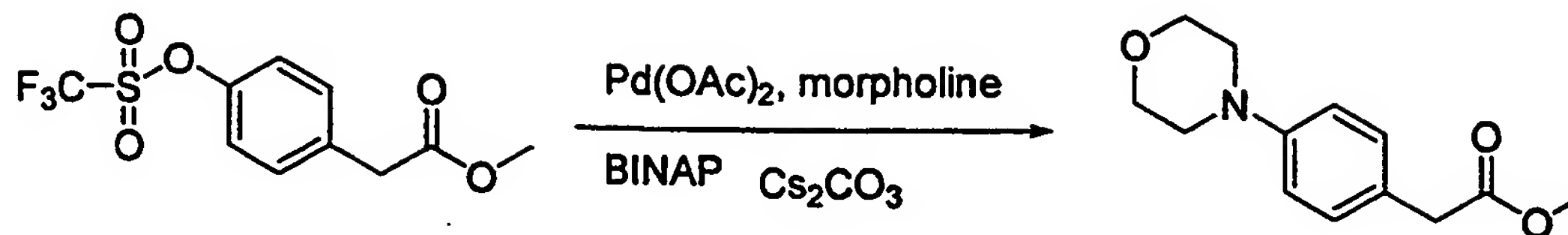
Prepared according to the general procedure outlined in Schemes 1 and 2. The starting materials were prepared as follows:

10 **Methyl-4-(trifluoromethylsulfonyloxy)phenyl acetate**

To methyl-4-hydroxyphenyl acetate (20 g, 120 mmol) and pyridine  
15 (20 mL, 240 mmol) in 100 mL dichloromethane at 0°C was added  
trifluoromethanesulfonic anhydride (23 mL, 132 mmol) dropwise over 30  
minutes. After an additional 30 minutes at 0°C followed by 30 minutes at  
ambient temperature, 1N hydrochloric acid was added and the reaction  
mixture was extracted into dichloromethane. The organic layer was  
20 washed with 1N hydrochloric acid, saturated sodium bicarbonate, brine,  
dried over magnesium sulfate, filtered, and concentrated providing 32 g  
(90%) of the title compound as a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 300 MHz)  
δ 7.38 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 3.72 (s, 3H), 3.66 (s,  
2H).

25

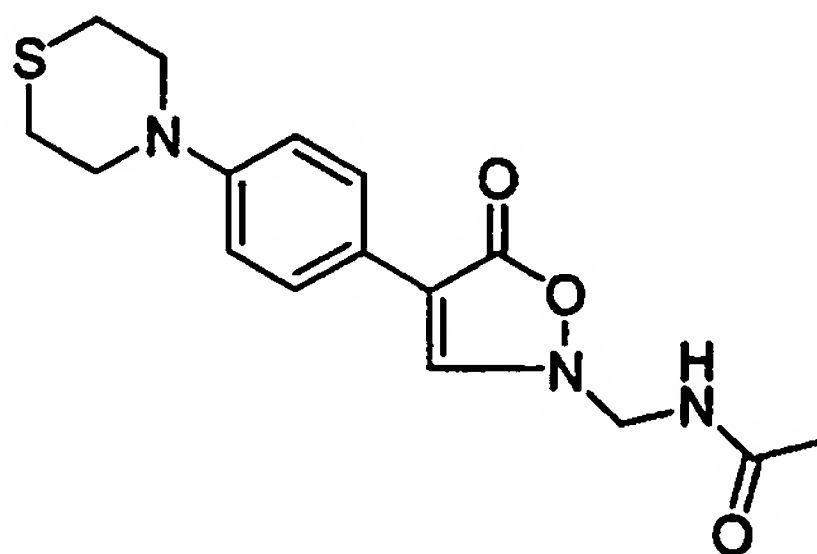
**Methyl-4-morpholinophenyl acetate**



Nitrogen was bubbled through a mixture of methyl-4-  
 5 (trifluoromethylsulfonyloxy)phenyl acetate (1.0 g, 3.35 mmol), cesium  
 carbonate (1.6 g, 4.69 mmol), palladium (II) acetate (22 mg, 0.10 mmol),  
 (S)-BINAP (93 mg, 0.15 mmol), and morpholine (0.35 mL, 4.02 mmol) in 8  
 mL toluene and the reaction mixture was heated to 80°C for 6 hours. The  
 reaction was then cooled, celite was added, and the mixture was  
 10 concentrated. Chromatography was performed on a Biotage flash 40i  
 chromatography module by loading the dried celite into a SIM and eluting  
 with 20% ethyl acetate / hexanes (40S cartridge) providing 250 mg (37%)  
 of the title compound as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 300 MHz) δ 7.19  
 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 3.89-3.85 (m, 4H), 3.69 (s,  
 15 3H), 3.56 (s, 2H), 3.17-3.13 (m, 4H).

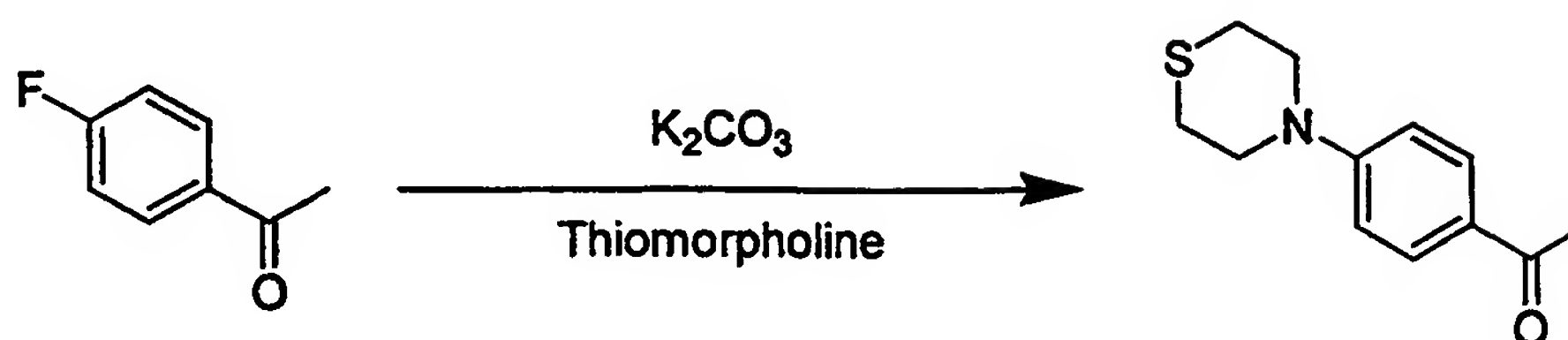
### EXAMPLE 28

N-{[4-(4-(1,4-thiazaperhydroin-4-yl)phenyl)-5-oxo-2-hydroisoxazol-2-  
 20 yl]methyl}acetamide



Prepared according to the general procedures outlined in Schemes  
 25 1 and 3. The starting materials were prepared as follows:

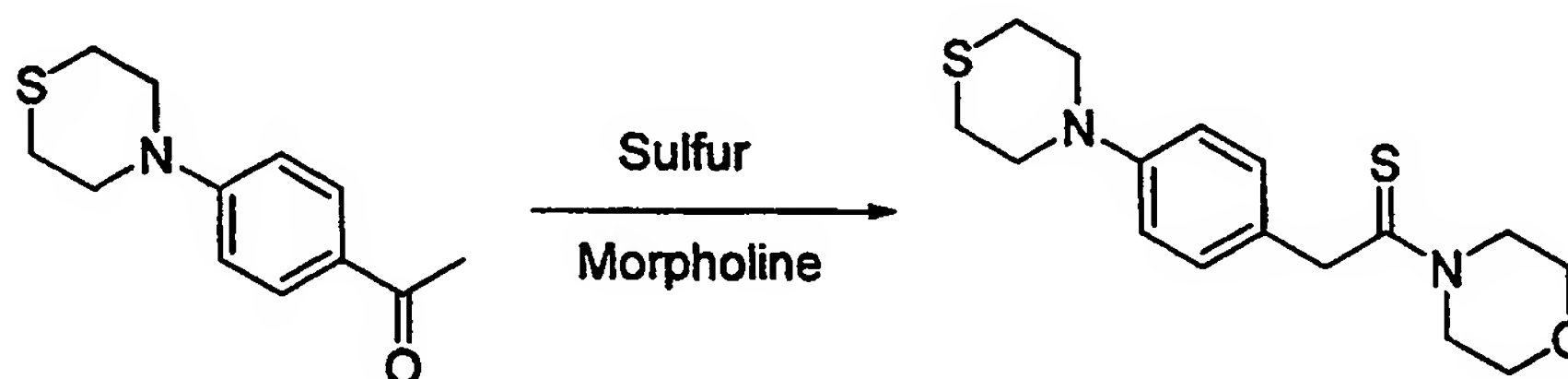
## 4-Thiomorpholinoacetophenone



5 To 4-fluoroacetophenone (20 g, 145 mmol) in 100 mL dimethylformamide was added potassium carbonate (39 g, 580 mmol) followed by thiomorpholine (87 mL, 870 mmol). The reaction mixture was heated to reflux and after 24 hours, it was cooled to ambient temperature and partitioned between water and dichloromethane. The organic layer  
10 was dried over magnesium sulfate, filtered, and concentrated. The residue was dissolved in ether and precipitated with hexanes providing 31 g (96%) of the title compound as a yellow solid.  $^1H$  NMR ( $CDCl_3$ ; 300 MHz)  $\delta$  7.87 (d,  $J = 9.0$  Hz, 2H), 6.82 (d,  $J = 9.0$  Hz, 2H), 3.81-3.78 (m, 4H), 2.73-2.69 (m, 4H), 2.53 (s, 3H).

15

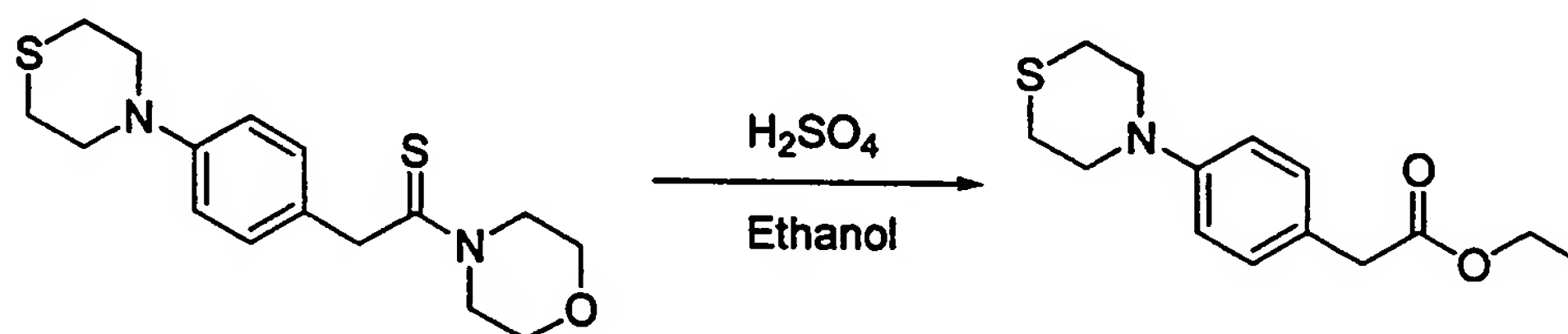
## 4-Thiomorpholinophenylthioacetomorpholide



20 A mixture of 4-thiomorpholinoacetophenone (30 g, 136 mmol), morpholine (16 mL, 180 mmol) and sulfur (6 g, 180 mmol) was heated to reflux for 6 hours, cooled to 50°C, and 100 mL 1:1 hexanes:ethyl acetate was added. The reaction mixture was again brought to reflux for 30 minutes, cooled, and the resultant orange precipitate was collected via  
25 filtration. The precipitate was washed with additional 1:1 ether / hexanes

providing 31 g (73%) of the title compound as a yellow-orange solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 300 MHz) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 2H), 4.35 (t, *J* = 4.8 Hz, 2H), 4.27 (s, 2H), 3.74 (t, *J* = 4.8 Hz, 2H), 3.65 (t, *J* = 4.2 Hz, 2H), 3.52 (t, *J* = 5.1 Hz, 4H), 3.41 (t, *J* = 5.4 Hz, 2H), 2.77-2.71 (m, 2H).

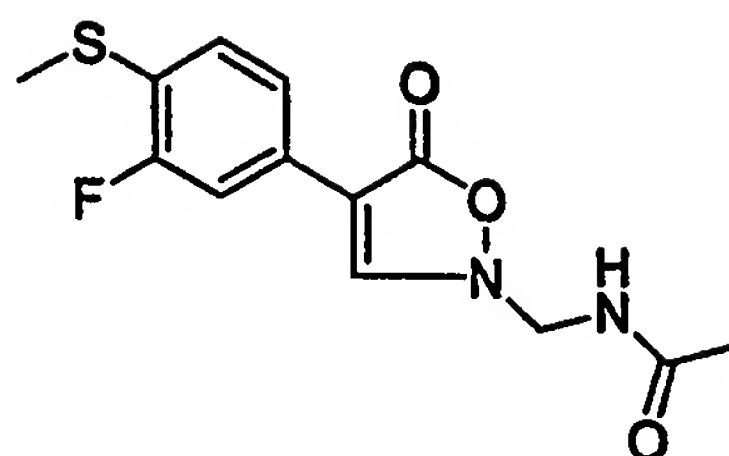
### Ethyl-4-thiomorpholinophenyl acetate



A solution of 4-thiomorpholinophenylthioacetomorpholide (30 g, 93.2 mmol) in 70 mL 1:1 ethanol:sulfuric acid was heated to reflux for 18 hours, cooled to room temperature and solid sodium bicarbonate was slowly added to the reaction until it reached pH 7. The reaction mixture was extracted with chloroform, and the organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated to a yellow residue. The residue was then dissolved in chloroform, loaded onto a Biotage flash 40i chromatography module (40M cartridge) and chromatographed with 10% ethyl acetate / hexanes providing 12 g (51%) of the title compound as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 300 MHz) δ 7.18 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.54-3.50 (m, 6H), 2.76-2.73 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H).

### EXAMPLE 29

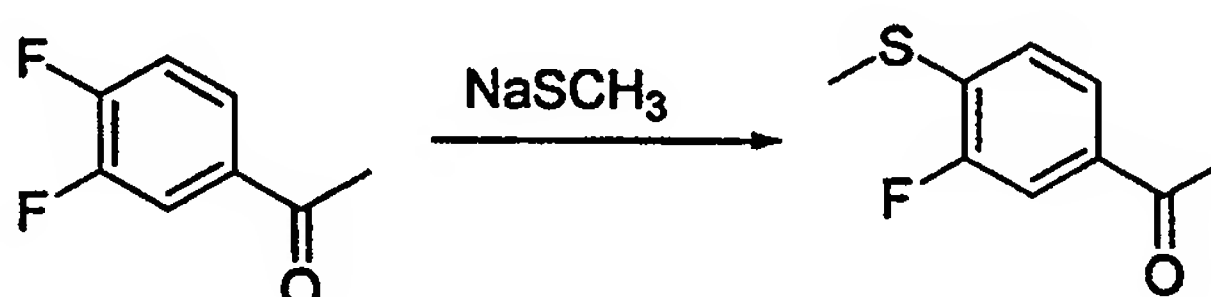
**N-[[4-(3-fluoro-4-methylthiophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide**



Prepared according to the general procedures outlined in Schemes 1 and 3. The starting materials were prepared as follows:

5

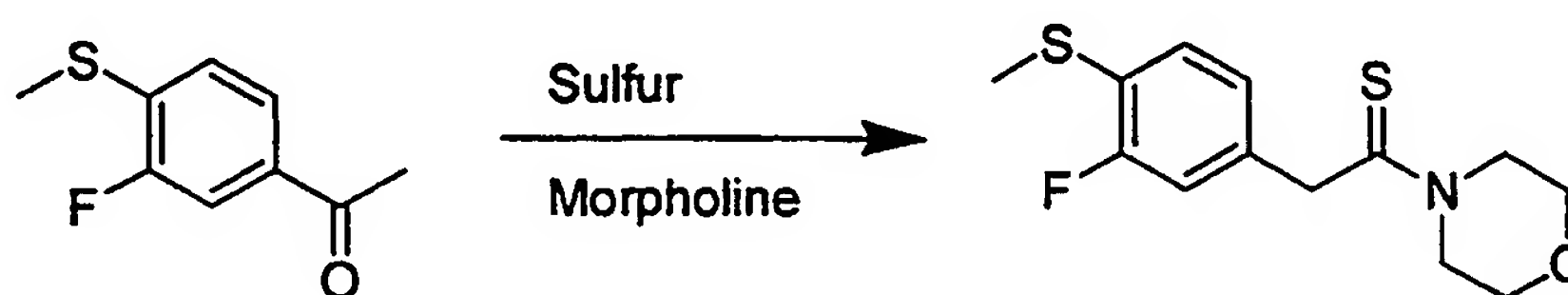
### 3-Fluoro-4-methylthioacetophenone



10 To 3, 4-difluoroacetophenone (30 g, 192 mmol) in 200 mL dimethylsulfoxide was added sodium thiomethoxide (15 g, 211 mmol). The reaction mixture was heated to 150°C for 2 hours and then partitioned between ethyl acetate and sodium bicarbonate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and  
15 concentrated. The residue was dissolved in ethyl acetate and precipitated with hexanes. The precipitate was collected by filtration providing 25 g (70%) of the title compound as a yellow solid.

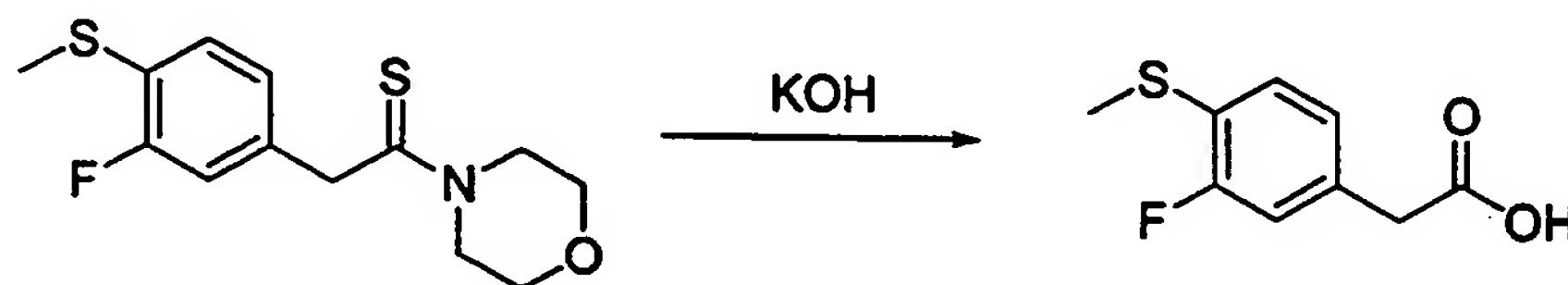
### 3-Fluoro-4-methylthiophenylthioacetomorpholide

20



A mixture of 3-fluoro-4-methylthioacetophenone (9.0 g, 48.9 mmol), morpholine (5.7 mL, 65.0 mmol), and sulfur (2.1 g, 65.0 mmol) were heated to reflux for 4 hours, cooled to 50°C, and 1:1 hexanes : ethyl acetate was added. The reaction mixture was again heated to reflux for 5 30 minutes, cooled to ambient temperature, and the resultant orange precipitate was collected by filtration. The precipitate was washed with 1:1 hexanes : ether providing 10.1 g (73%) of the title compound as a yellow-orange solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>; 300 MHz) δ 7.36-7.29 (m, 1H), 7.20-7.15 (m, 2H), 4.27 (s, 2H), 4.22 (t, *J* = 4.8 Hz, 2H), 3.73 (t, *J* = 4.5 Hz, 2H), 3.65 (t, *J* = 4.8 Hz, 2H), 3.47 (t, *J* = 5.1 Hz, 2H), 2.47 (s, 3H).

#### 3-Fluoro-4-methylthiophenylacetic acid



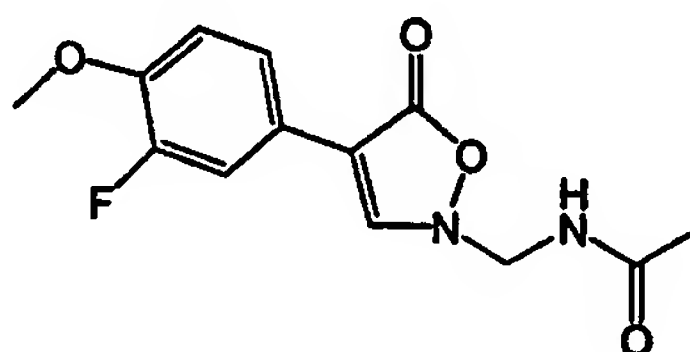
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To 3-fluoro-4-methylthiophenylthioacetomorpholine (2.6 g, 90.9 mmol) was added 500 mL 10% potassium hydroxide. The reaction mixture was heated to reflux for 3 hours, cooled to ambient temperature, and adjusted to pH 4 by the careful addition of 2N hydrochloric acid. The aqueous solution was extracted with dichloromethane and the organic layer was then extracted with 200 mL 10% potassium hydroxide. The aqueous layer was then brought to pH 4 by the careful addition of 2N hydrochloric acid and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered, and concentrated providing 10.0 g (55%) of the title compound as a brown oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 300 MHz) δ 7.24-7.21 (m, 1H), 7.04-6.99 (m, 2H), 3.63 (s, 2H), 2.46 (s, 3H).



**EXAMPLE 30****N-{[4-(3-fluoro-4-methoxyphenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide**

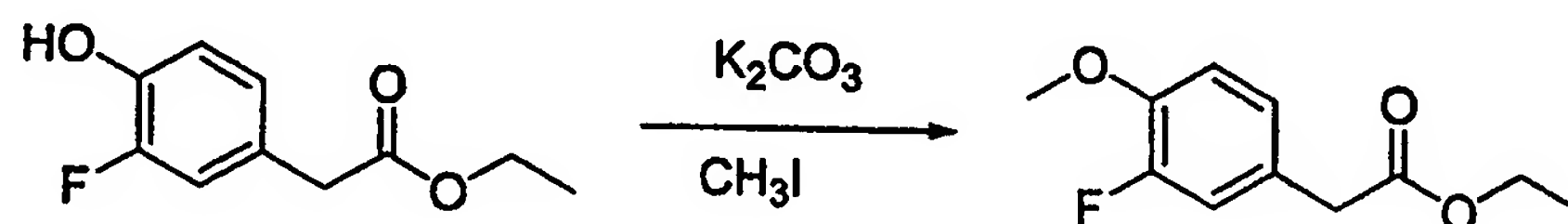
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Prepared according to the general procedure outlined in Schemes  
1. The starting material was prepared as follows:

10

Ethyl-(3-Fluoro-4-methoxy)phenyl acetate



15

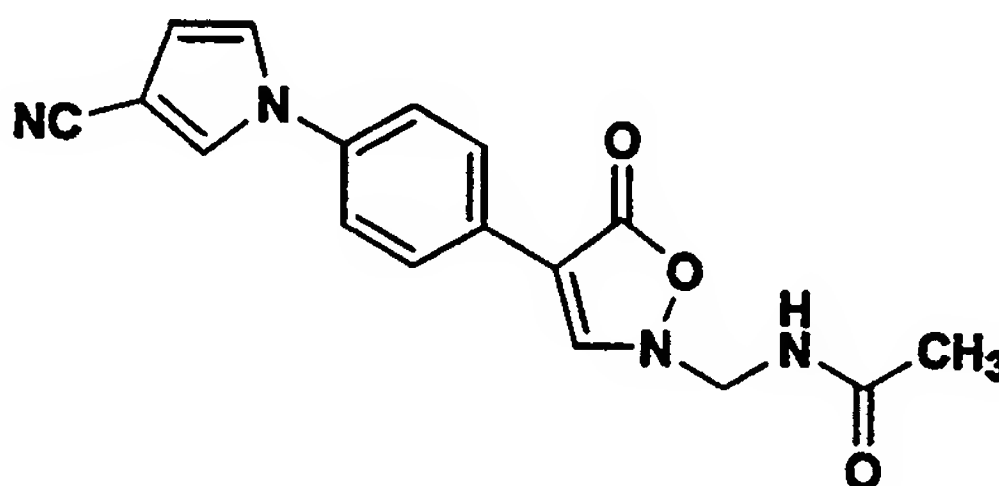
To ethyl-(3-fluoro-4-hydroxy)phenyl acetate (2.5 g, 8.9 mmol) in 20mL acetone was added potassium carbonate (3.4 g, 24.2 mmol) and iodomethane (1.5 mL, 24.2 mmol). The reaction mixture was heated to reflux for 2 hours, cooled, and partitioned between saturated sodium bicarbonate and ether. The organic layer was washed with brine, dried  
20 over magnesium sulfate, filtered and concentrated providing 2.3 g (88%) of the title compound as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 300 MHz) δ 7.06-6.88 (m, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 3.54 (s, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).



**EXAMPLE 31**

**N-({4-[4-(3-cyanopyrrolyl)phenyl]-5-oxo-2-hydroisoxazol-2-yl}methyl)acetamide**

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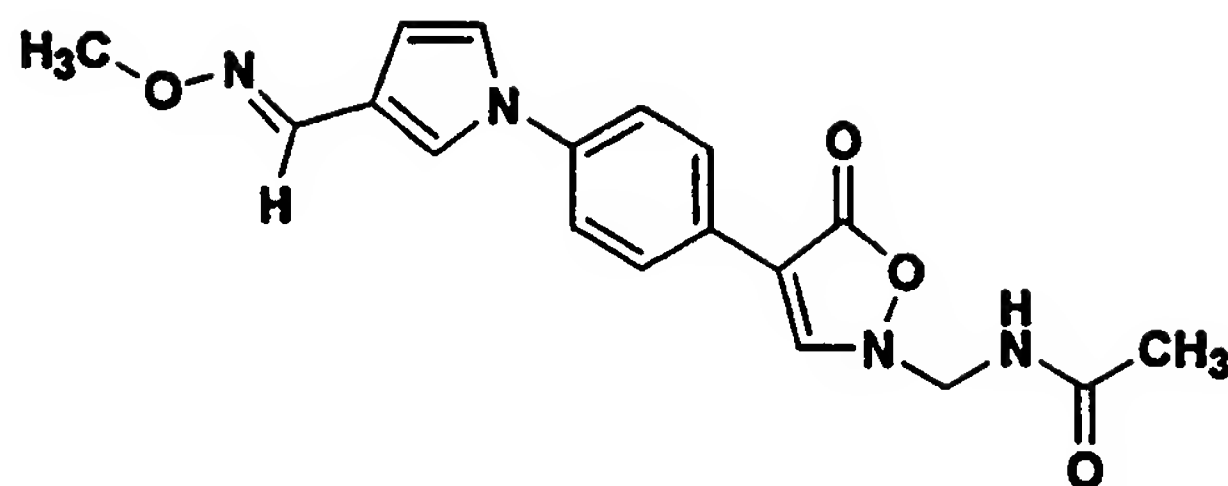


To a mixture of N-[(4-{4-[3-((hydroxyimino)methyl)pyrrolyl]phenyl}-5-oxo-2-hydroisoxazol-2-yl)methyl]acetamide (100 mg, 0.29 mmol) in 3 ml  
10 of CH<sub>3</sub>CN and 1 ml of CCl<sub>4</sub> was added polymer-bound triphenylphosphine (400 mg, 1.2 mmol) and the mixture was heated at reflux for 8 hours. It was then dissolved in ethyl acetate, filtered, and concentrated to yield a yellow solid. This solid was then triturated with ether to obtain 30 mg (32 %) of the title compound as a yellow solid. <sup>1</sup>H  
15 NMR (300 MHz, DMSO-d<sub>6</sub>) δ 9.08 (s, 1 H), 8.97 (t, J = 6 Hz, 1 H), 8.28, (s, 1 H), 7.92 (d, J = 9 Hz, 2 H), 7.70 (d, J = 9 Hz, 2 H), 7.59 (m, 1 H), 6.74 (m, 1 H), 5.06 (d, J = 6 Hz, 2 H), 1.86 (s, 3 H).

**EXAMPLE 32**

20

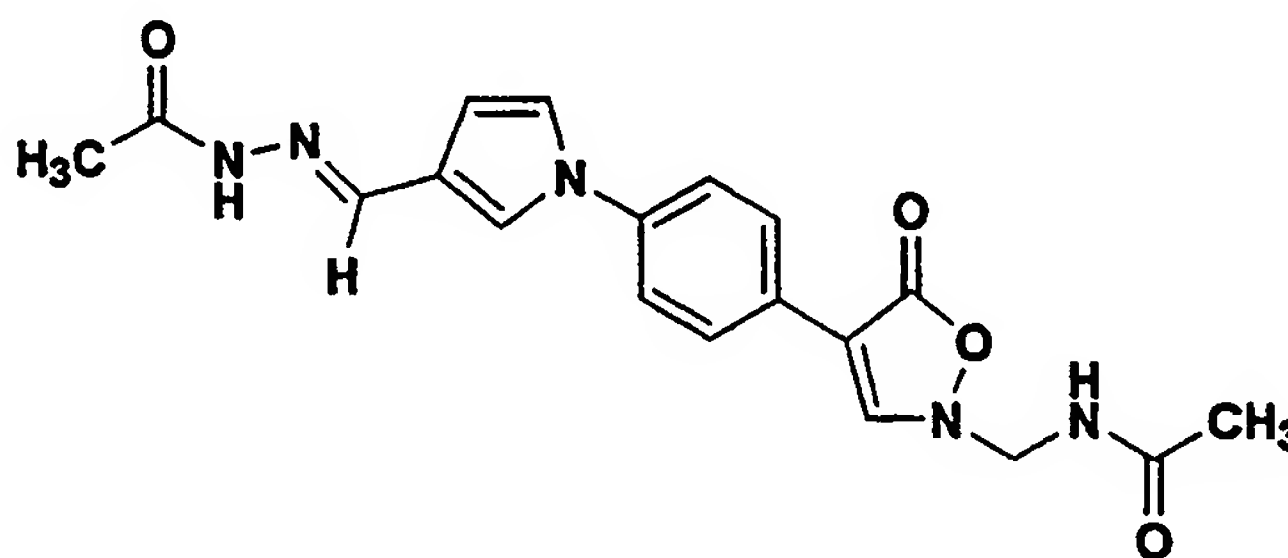
**N-[(4-{4-[3-((1E)-2-aza-2-methoxyvinyl)pyrrolyl]phenyl}-5-oxo-2-hydroisoxazol-2-yl)methyl]acetamide**



A mixture of N-({4-[4-(3-formylpyrrolyl)phenyl]-5-oxo-2-hydroisoxazol-2-yl}methyl)acetamide (100 mg, 0.3 mmol), HCl·NH<sub>2</sub>OCH<sub>3</sub> (31 mg, 0.37 mmol) and sodium carbonate (20 mg, 0.19 mmol) was dissolved in 3 mL of MeOH and 2 mL of water. To this mixture was added acetic acid to adjust the pH to 5. The reaction was heated at reflux for 1 hour. The reaction was cooled to room temperature, and the yellow precipitate was collected by filtration to give 40 mg (36 %) of the title compound as a yellow solid. (M+H<sup>+</sup>)= 355.

### EXAMPLE 33

N-([4-(4-{3-[(1E)-2-(acetylamino)-2-azavinyl]pyrrolyl}phenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl)acetamide

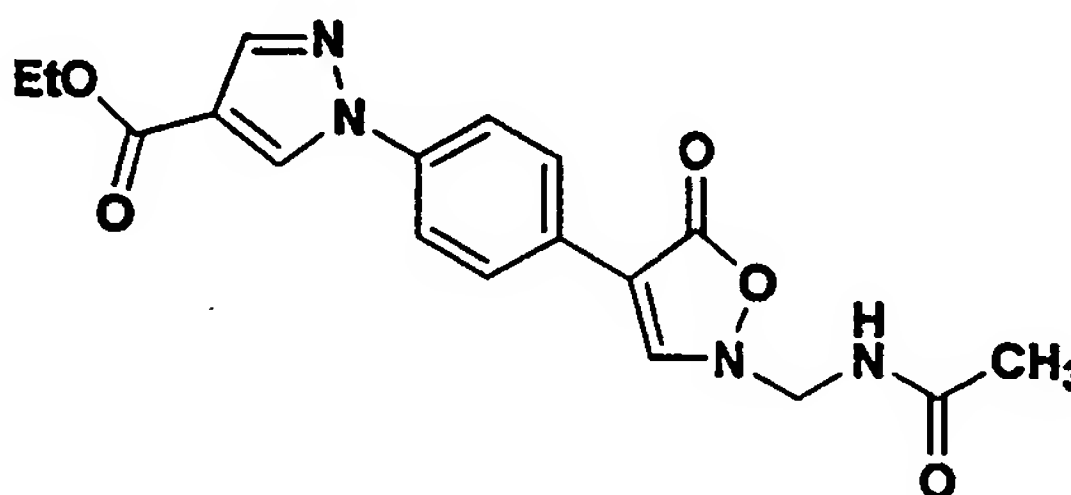


A mixture of N-({4-[4-(3-formylpyrrolyl)phenyl]-5-oxo-2-hydroisoxazol-2-yl}methyl)acetamide (100 mg, 0.30 mmol) and acetic hydrazide (28 mg, 0.38 mmol) in 3 mL of EtOH was heated at reflux for 1 hour. The reaction was cooled to room temperature, and the yellow

precipitate was collected by filtration to give 80mg (36 %) of the title compound. (M+H<sup>+</sup>)=382.

### EXAMPLE 34

5 Ethyl 1-(4-{2-[(acetylamino)methyl]-5-oxo-2-hydroisoxazol-4-yl}phenyl)pyrazole-4-carboxylate

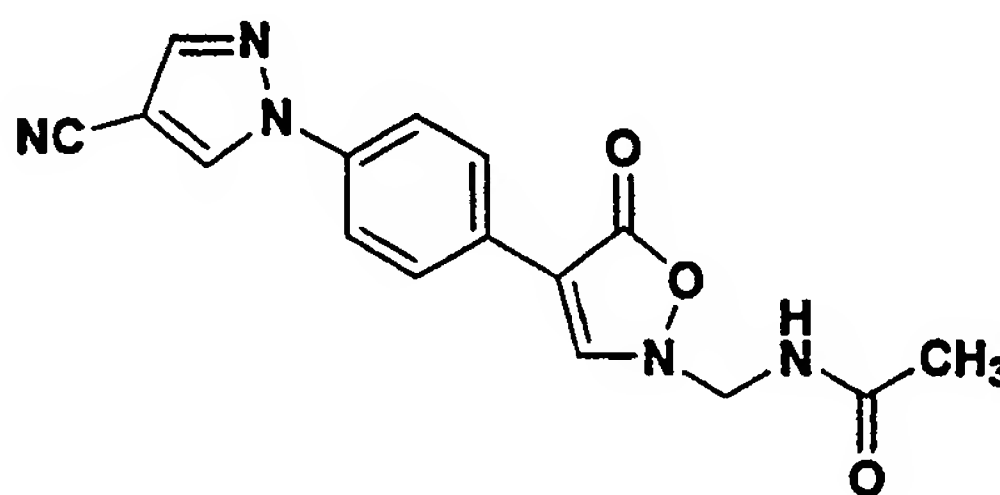


10 To a mixture of N-[[4-(4-hydrazinylphenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl]acetamide hydrochloride (150 mg, 0.5 mmol) in 3 mL of methanol was added sodium bicarbonate (50 mg, 0.6 mmol) and ethoxycarbonylmalondialdehyde (75 mg, 0.52 mmol). The mixture was stirred at room temperature overnight. The solid was collected by filtration  
15 and then washed with water, and dried to yield 140 mg of a purple solid. The crude product was subjected to silica gel chromatography (eluting with ethyl acetate followed by 5% methanol/ethyl acetate) to yield 123 mg (66%) of the title compound as a yellow solid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 9.11 (s, 1 H), 9.08 (s, 1 H), 8.96 (t, J = 6 Hz, 1 H), 8.15 (s, 1 H), 7.95  
20 (m, 4 H), 5.06 (d, J = 6 Hz, 2 H), 4.28, (q, J = 7 Hz, 2 H), 1.86 (s, 3 H), 1.31 (t, J = 7 Hz, 3 H).

The starting material, N-[[4-(4-hydrazinylphenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl]acetamide hydrochloride, was prepared as  
25 follows. Sodium nitrite (112 mg, 1.6 mmol) in 2 mL of water was added to a solution of N-[[4-(4-aminophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl]acetamide (400 mg, 1.6 mmol) in concentrated hydrochloric acid

at 0°C over 5 minutes. The reaction was stirred for an additional 10 minutes at 0°C, and then SnCl<sub>2</sub>·2H<sub>2</sub>O (720 mg, 3.2 mmol) in 2 mL of concentrated hydrochloric acid was added. This mixture was stirred at room temperature for 3 hours. The reaction mixture was then filtered to collect a yellow solid which was washed with 3 mL of water and dried to yield 260 mg (55%) of the title compound. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.2 (s, 2 H), 8.94 (t, *J* = 6 Hz, 1 H), 8.82, (s, 1 H), 8.35 (s, 1 H), 7.70 (d, *J* = 9, 2 H), 6.99 (d, *J* = 9, 2 H), 4.99 (d, *J* = 6 Hz, 2 H), 1.84 (s, 3 H).

10

**EXAMPLE 35****N-({4-[4-(4-cyanopyrazolyl)phenyl]-5-oxo-2-hydroisoxazol-2-yl}methyl)acetamide**

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To a mixture of N-{{4-[4-(4-hydrazinylphenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide hydrochloride (50 mg, 0.17 mmol) in 2 mL of methanol was added 20 mg (0.24 mmol) of sodium bicarbonate and cyanomalondialdehyde (30 mg, 0.3 mmol). The mixture was stirred at room temperature overnight. It was then concentrated to give a solid which was washed with water then methanol to give 42 mg (76%) of the title compound as a yellow solid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 9.35 (s, 1 H), 9.10 (s, 1 H), 8.98 (t, *J* = 6 Hz, 1 H), 8.37 (s, 1 H), 7.93 (m, 4 H), 5.07 (d, *J* = 6 Hz, 2 H), 1.86 (s, 3 H).

25

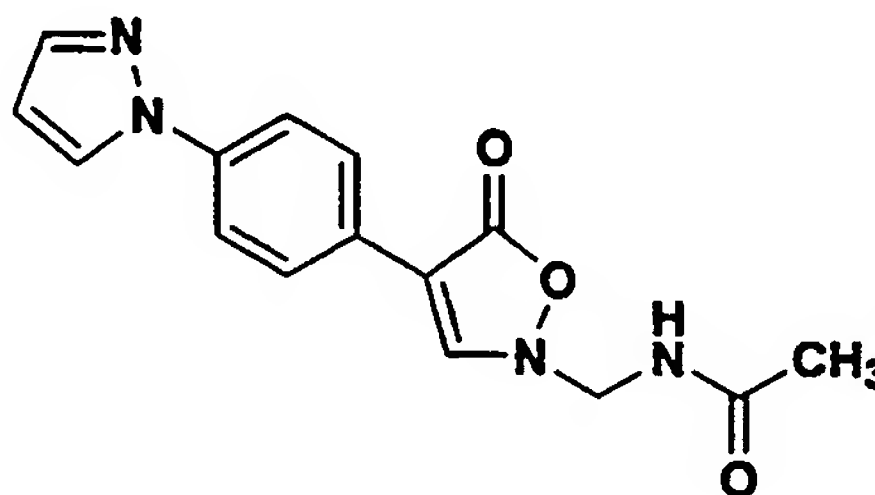
Preparation of cyanomalondialdehyde. To a dried flask was added sodium hydride (0.82 g, 50% suspended in mineral oil, 17 mmol). The sodium hydride was washed three times with 15 mL of ether, and then 15 mL of ether was added to the flask. After cooling the slurry to 0°C, ethyl  
5 formate (10.4 g, 140 mmol) was added. To this mixture was added 3,3-diethoxypropionitrile (2 g, 14 mmol) in 10 ml of ether over 2 hours (syringe pump). The mixture was stirred at room temperature for 20 hours, and then poured into 100 mL of ice water. This solution was extracted three times with ether, and then the ether extracts were discarded. The  
10 aqueous phase was acidified to pH 3 with concentrated HCl and extracted with dichloromethane. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated to yield 0.3 g of cyanomalondialdehyde as a yellow solid. Additional product was recovered from the pH 3 aqueous phase: the aqueous phase was  
15 concentrated to dryness, and then dissolved in 5 mL of methanol. The inorganic salt was removed by filtration, and the filtrate was concentrated to yield 1 g of cyanomalondialdehyde as a yellow solid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.94 (s, 2 H), 4.95 (br s, 1 H).

20

### EXAMPLE 36

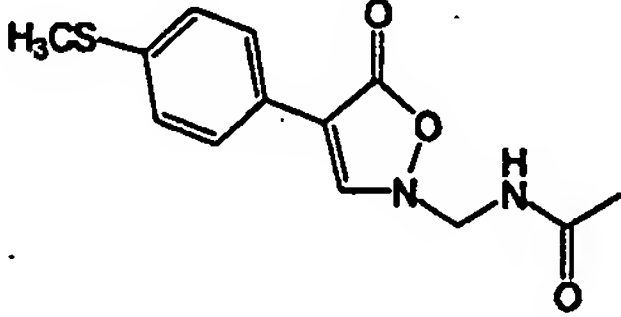
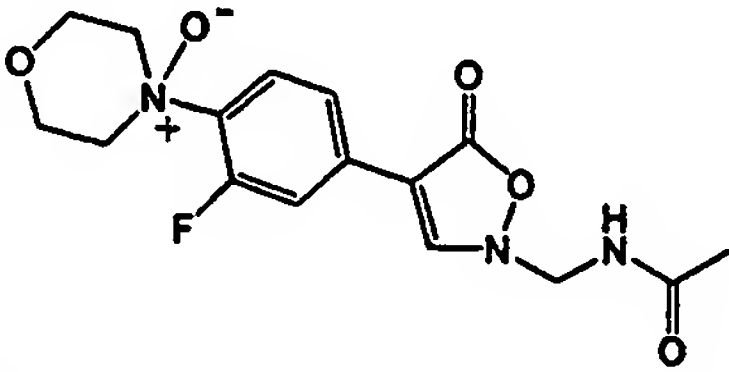
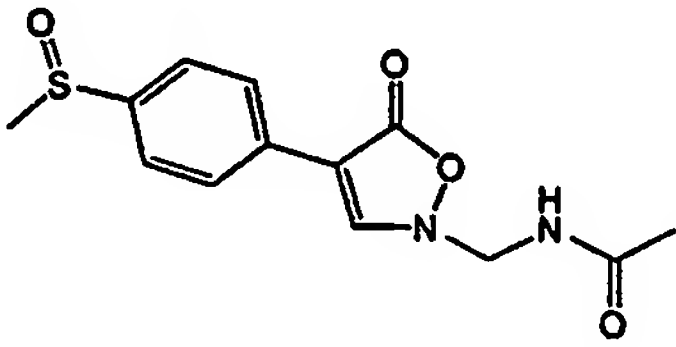
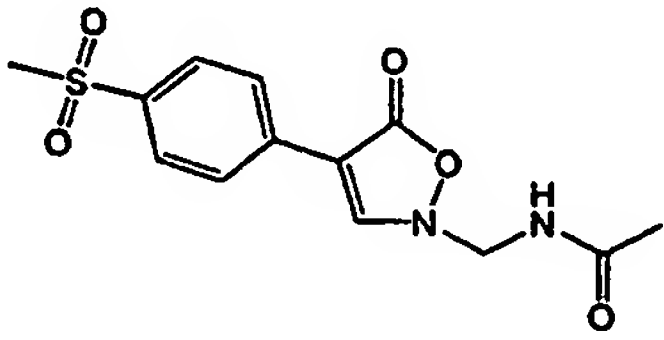
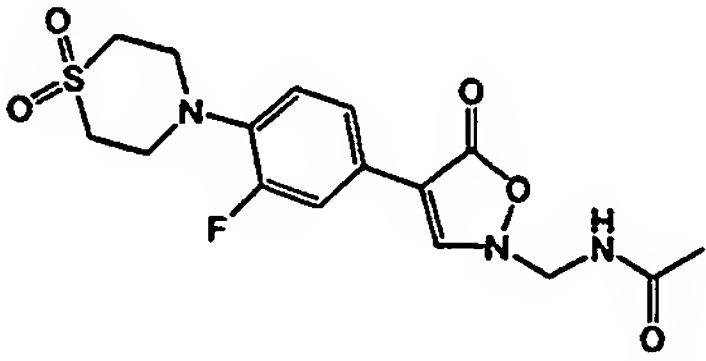
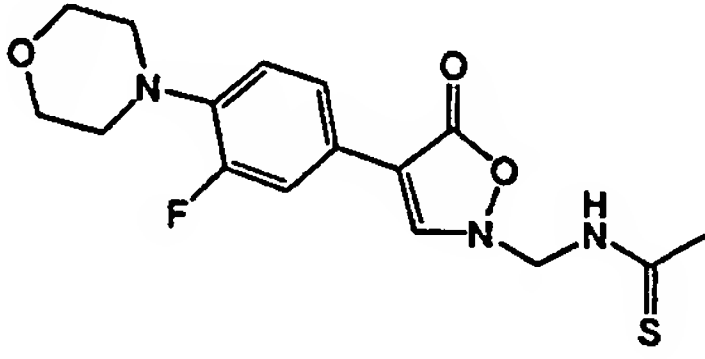
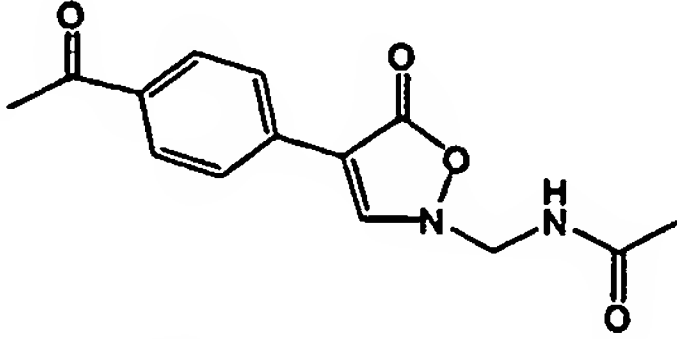
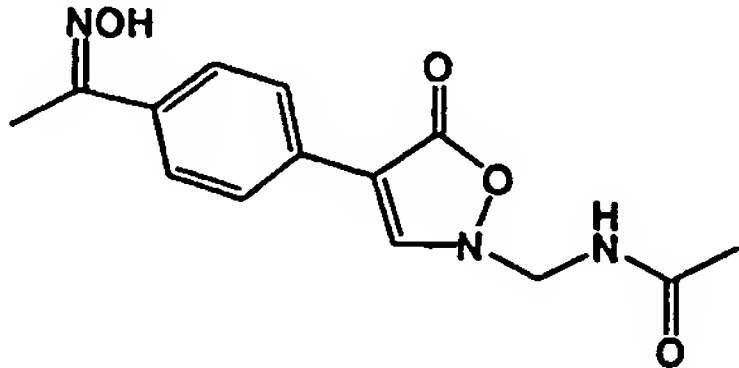
N-{[5-oxo-4-(4-pyrazolylphenyl)-2-hydroisoxazol-2-yl]methyl}acetamide

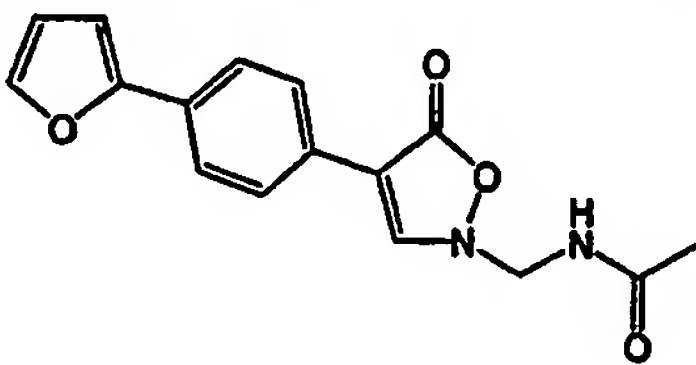
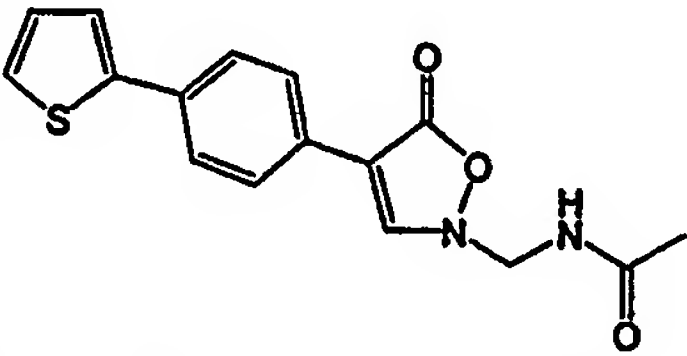
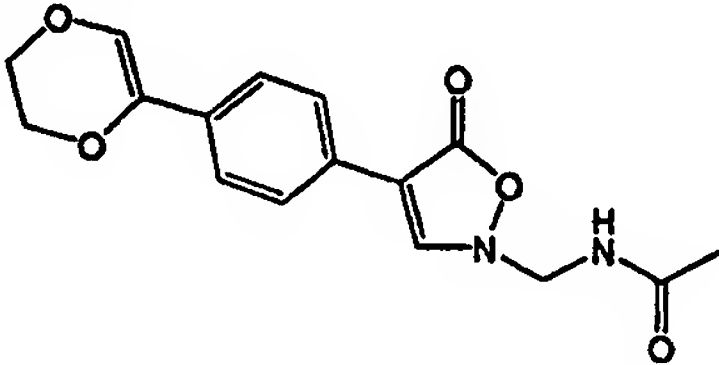
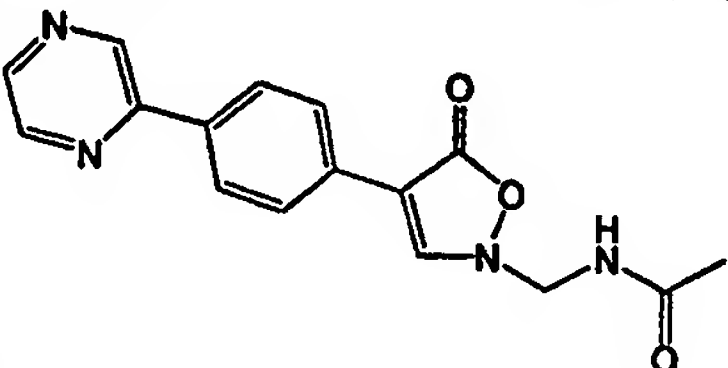
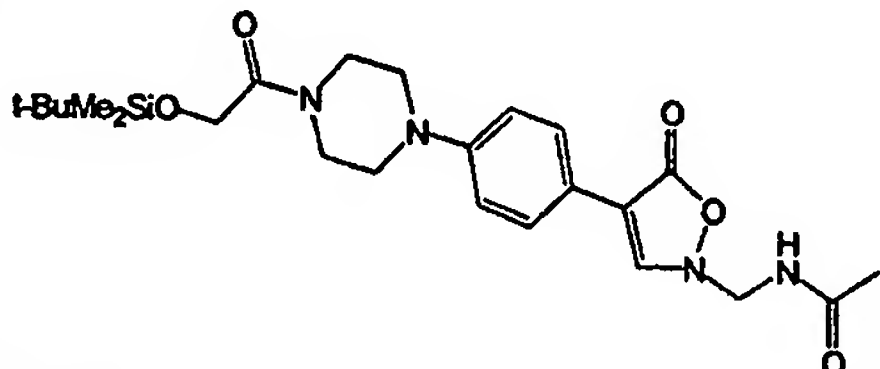
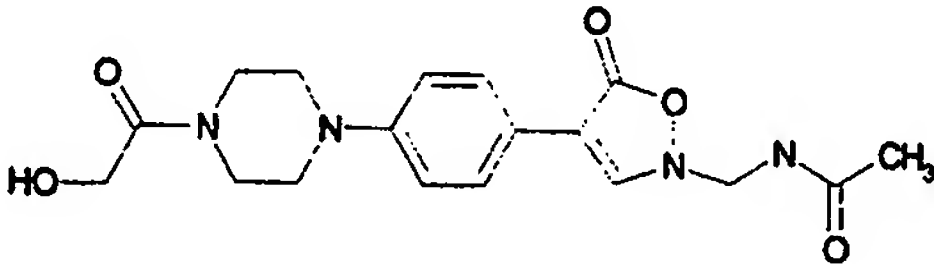
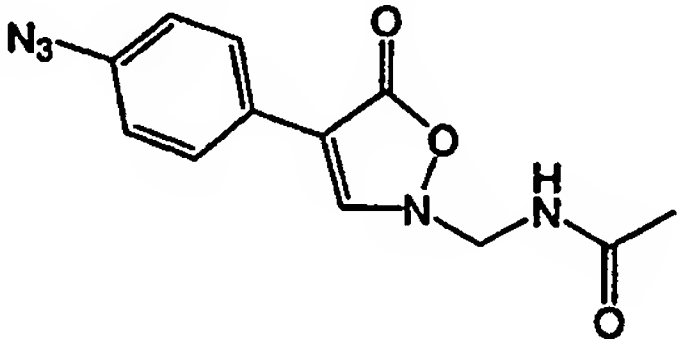
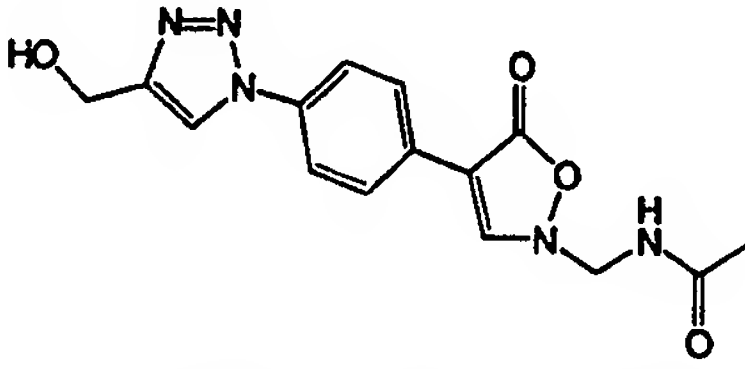
25



To a mixture of N-[[4-(4-hydrazinylphenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl]acetamide hydrochloride (100 mg, 0.33 mmol) in 3 mL of methanol was added sodium bicarbonate (28 mg, 0.33mmol) and malondialdehyde (50 mg, 0.35 mmol). The mixture was stirred at room temperature overnight. It was then concentrated to yield 120 mg of a yellow oil, which was then purified by silica gel chromatography (eluting with ethyl acetate) to obtain 30 mg (30%) of the title compound as a yellow solid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 9.03 (s, 1 H), 8.95 (t, *J* = 6 Hz, 1 H), 8.52 (s, 1 H), 7.88 (m, 4 H), 7.75 (s, 1 H), 6.56 (s, 1 H), 5.05 (d, *J* = 6 Hz, 2 H), 1.86 (s, 3 H).

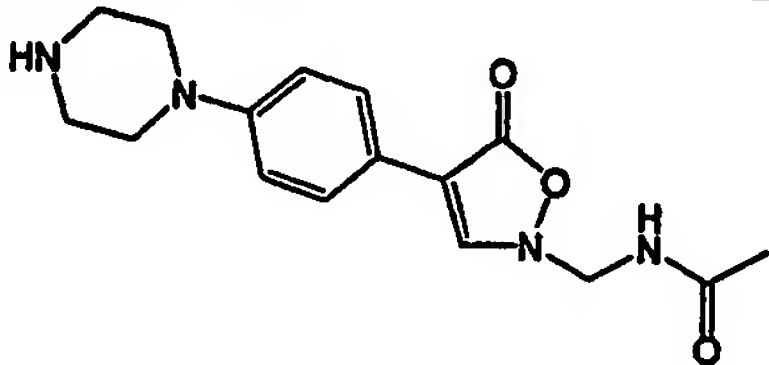
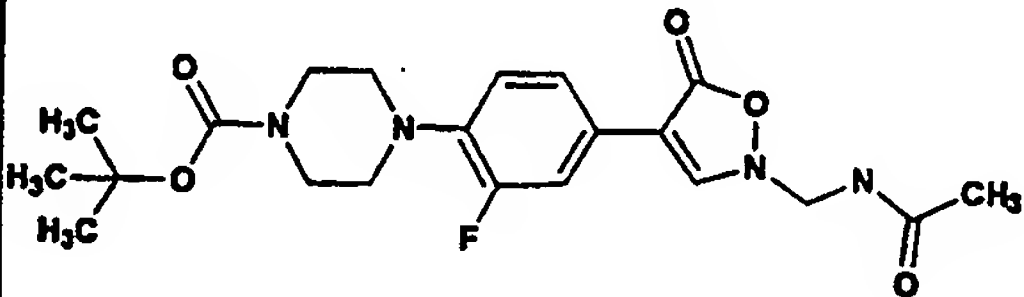
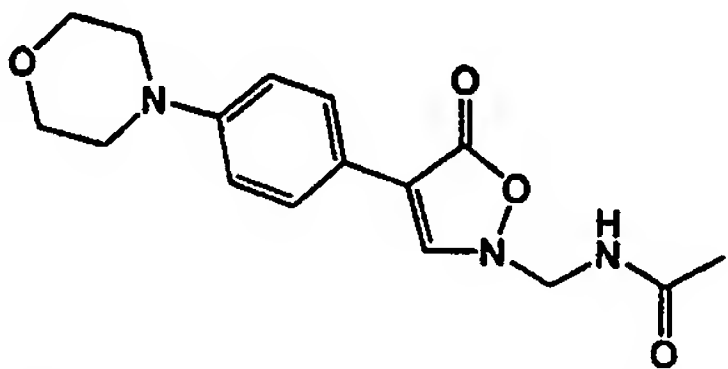
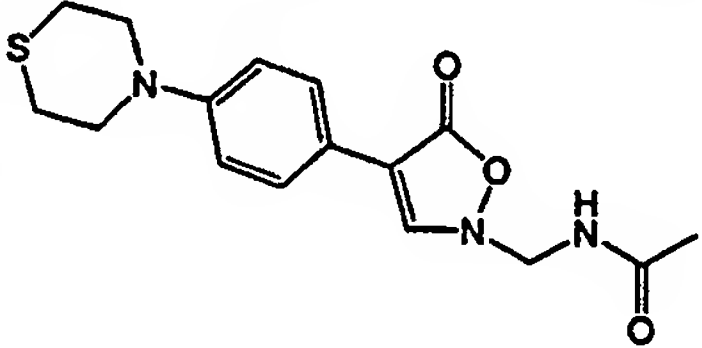
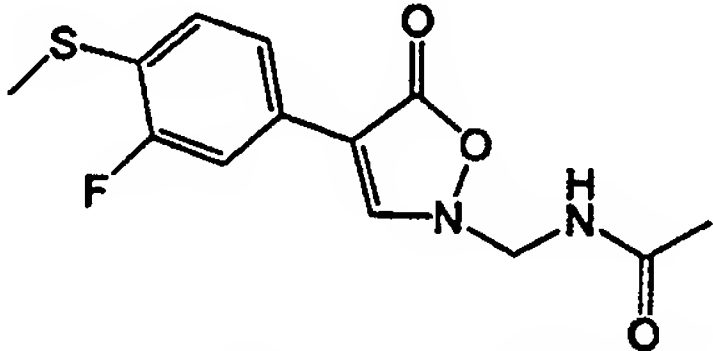
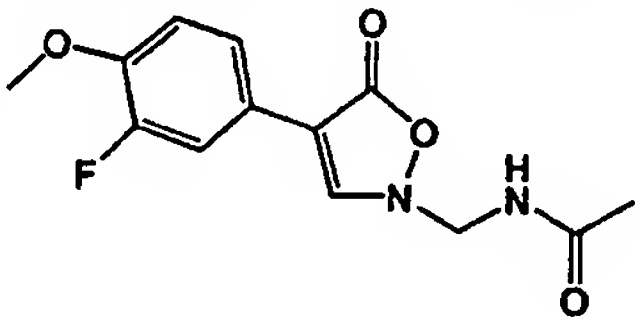
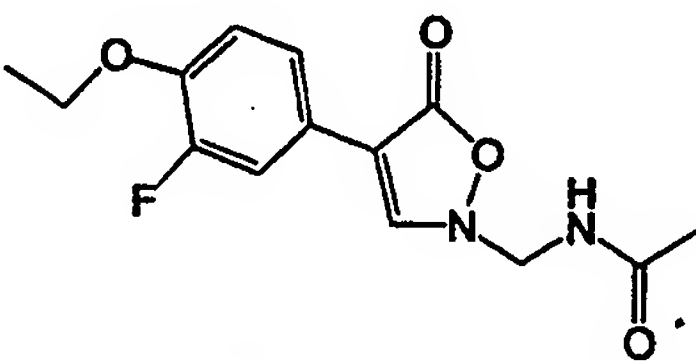
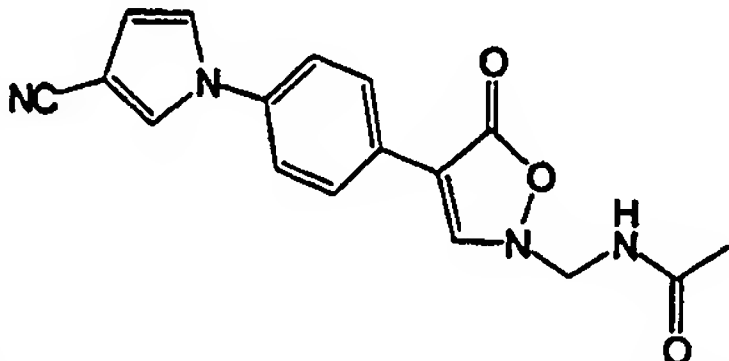
The table below shows the chemical structures, characterizing properties (MS data) and preparative method for several representative compounds of the present invention, including those of Examples 1-36 described above.

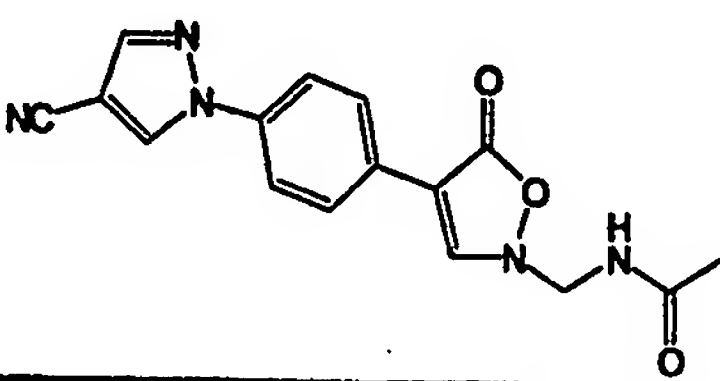
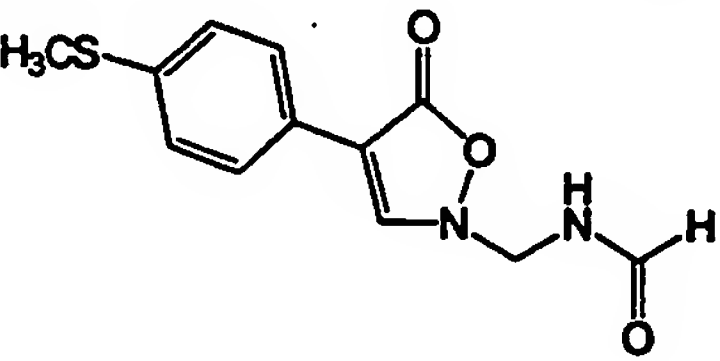
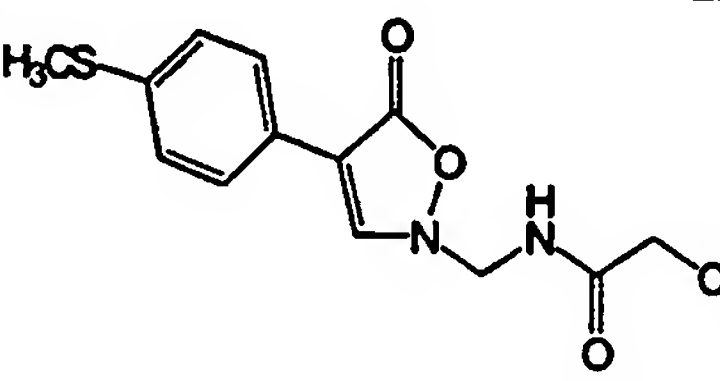
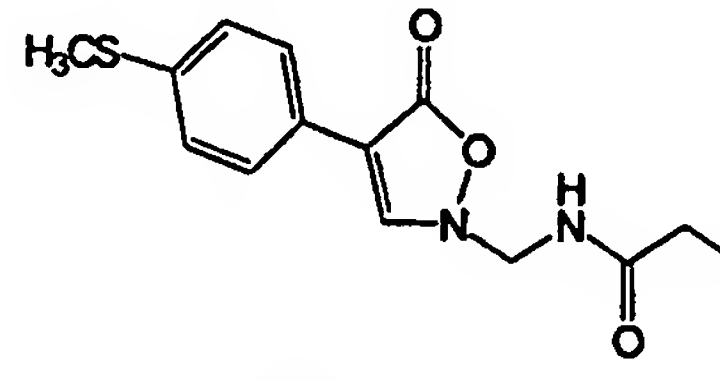
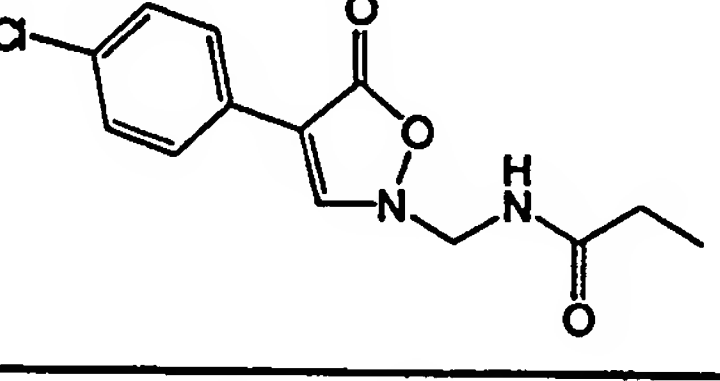
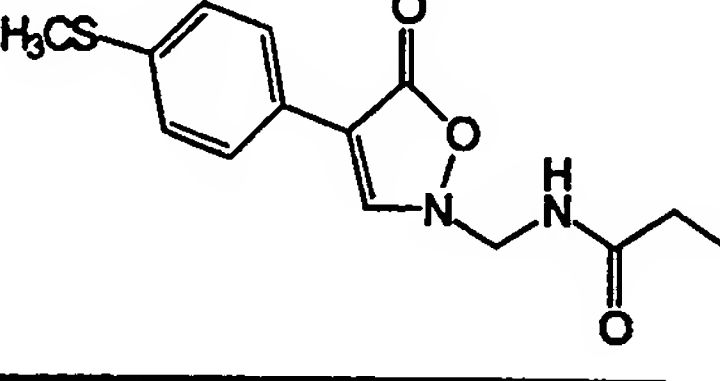
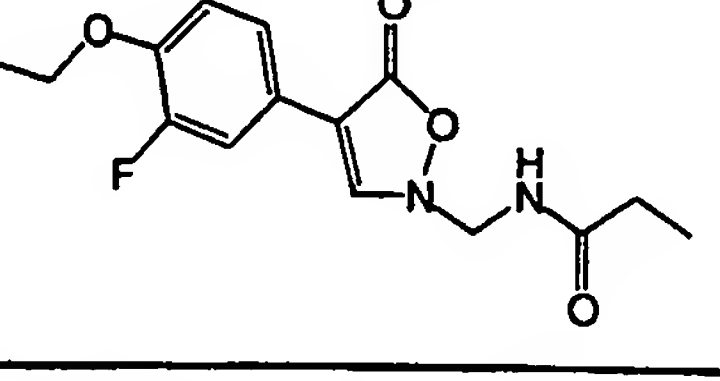
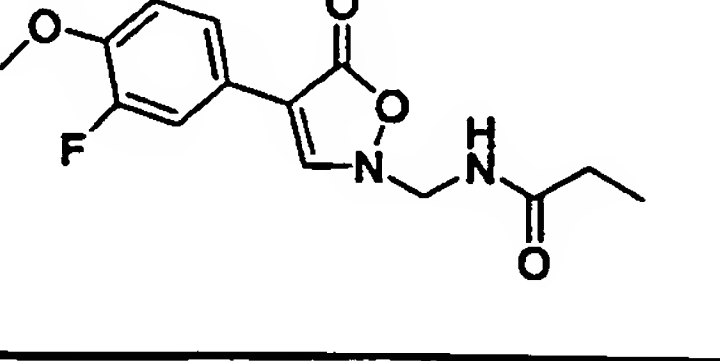
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4		(M+H)+ = 311 ESI	1, 4
5		(M+H)+ = 384 ESI	3, 1, 4
6		(M+H)+ = 352 ESI	3, 1, 9
7		(M+H)+ = 275 ESI	1
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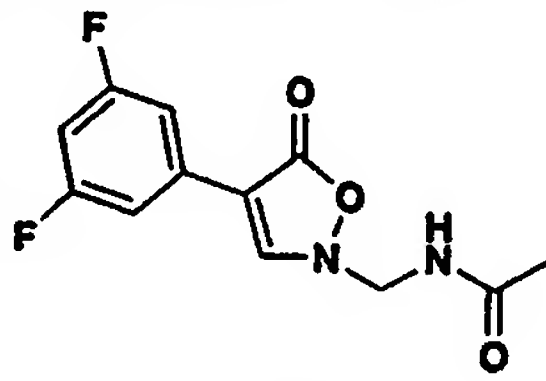
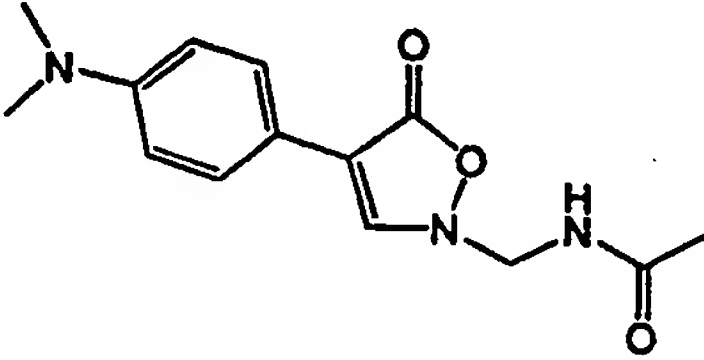
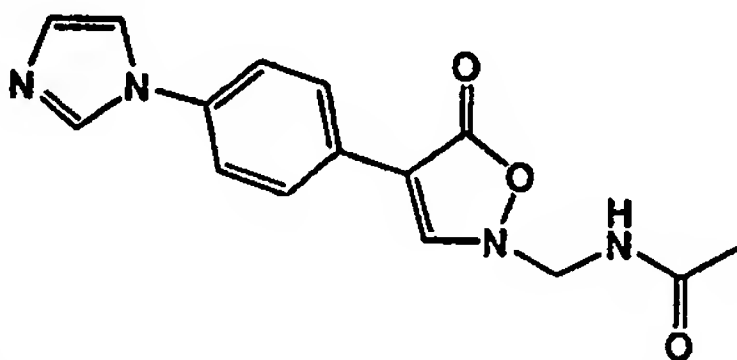
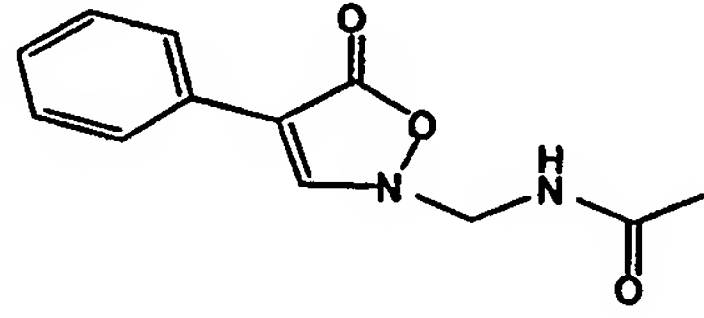
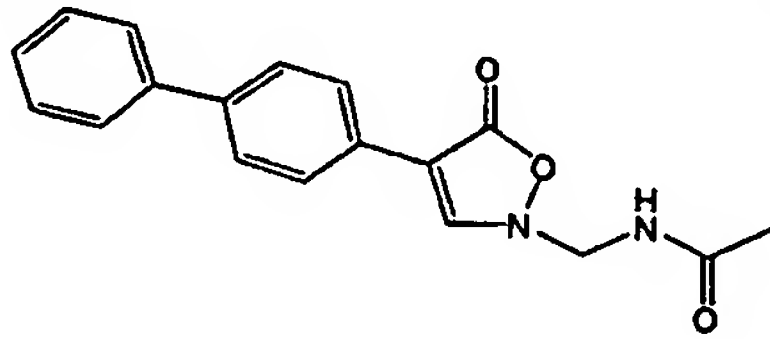
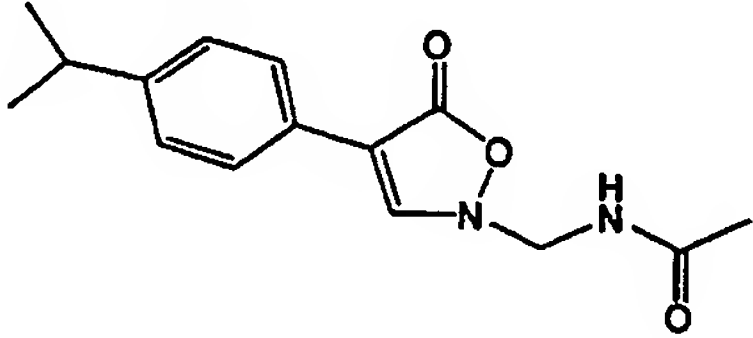
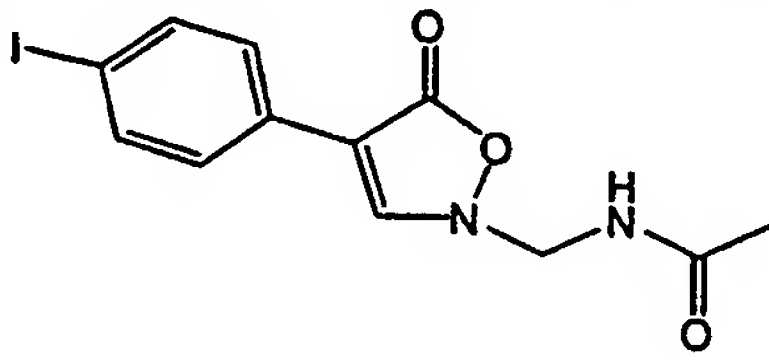
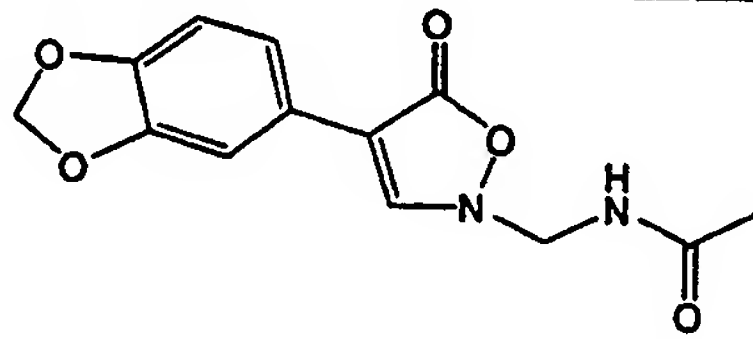
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12		(M+H) <sup>+</sup> = 311 ESI	1, 5
13		(M+H) <sup>+</sup> = 489 ESI	2, 1, 6
14		(M+H) <sup>+</sup> = 375 ESI	2, 1, 6
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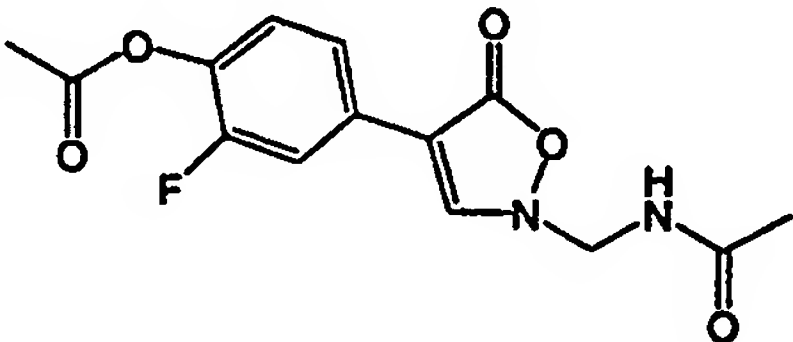
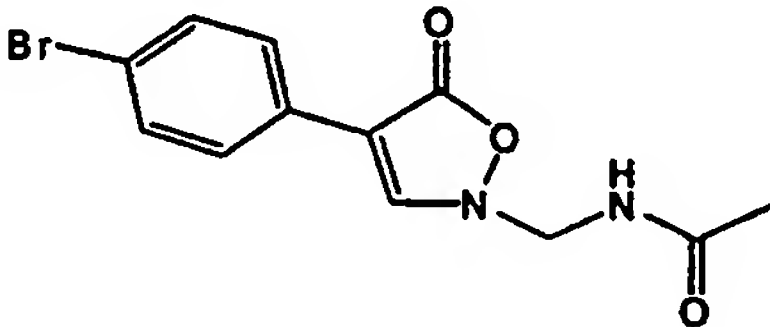
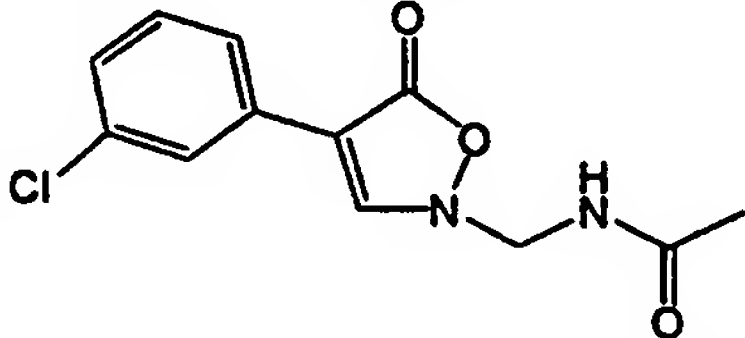
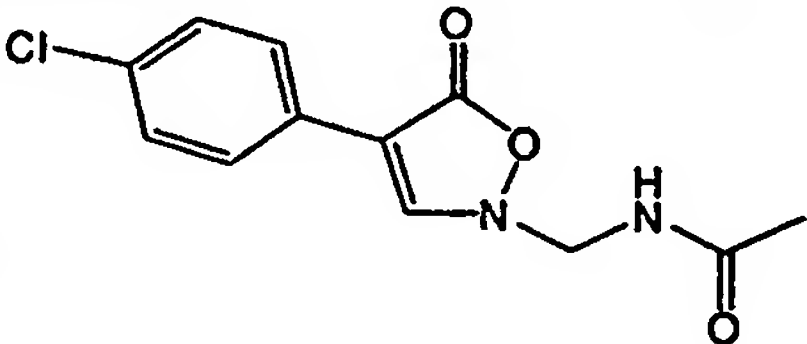
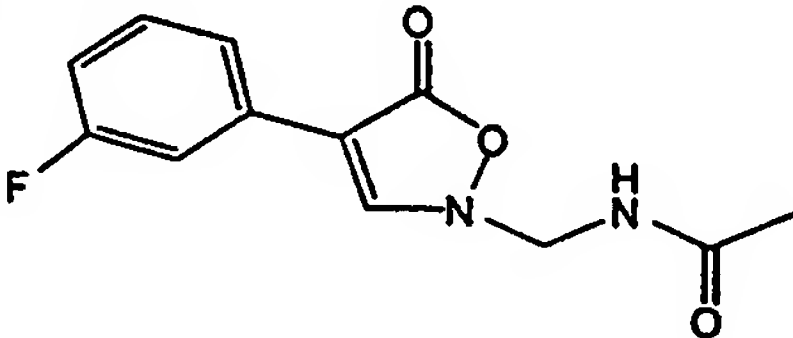
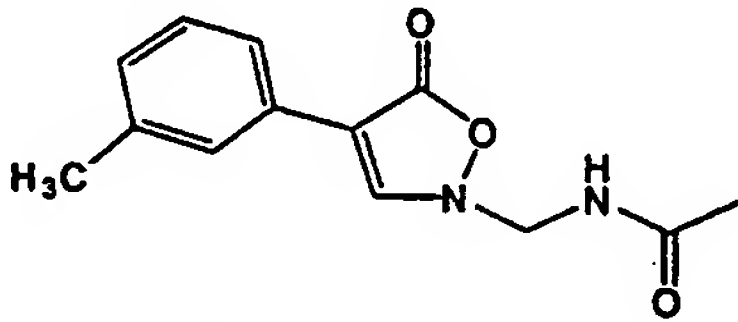
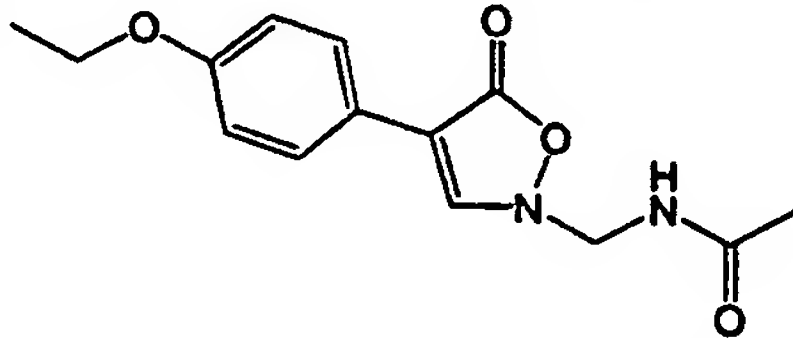
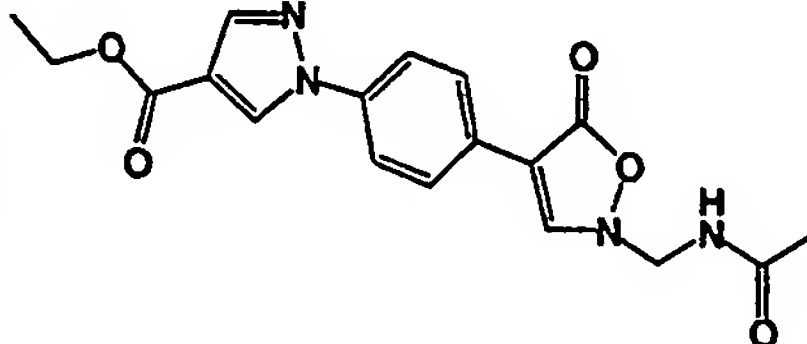


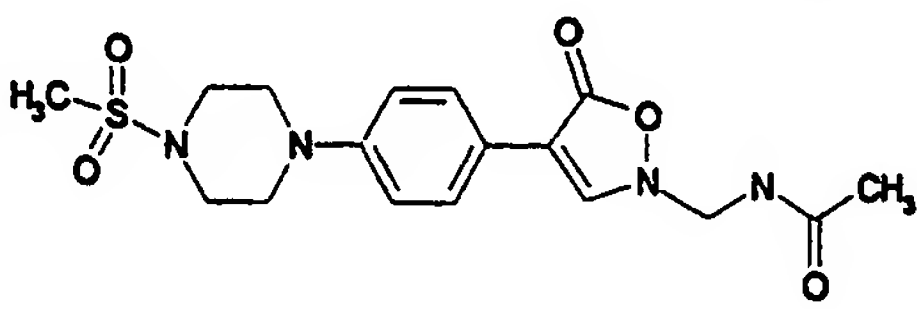
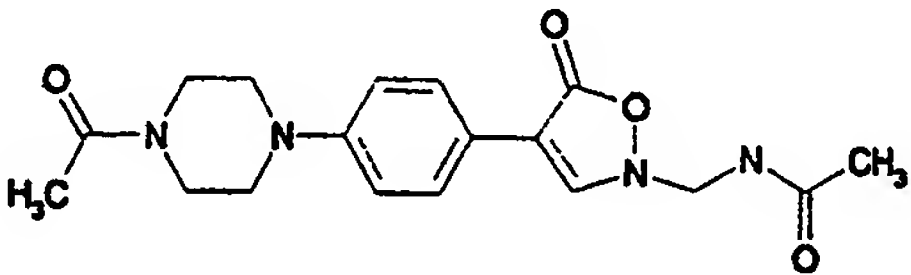
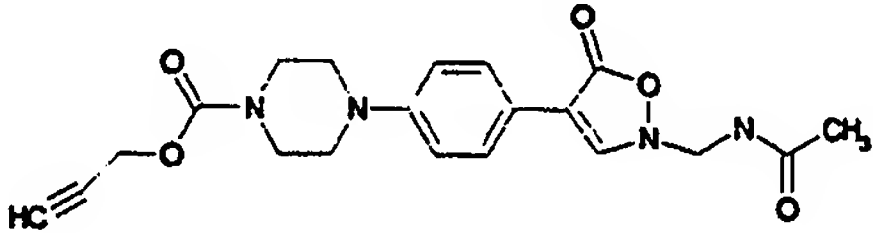
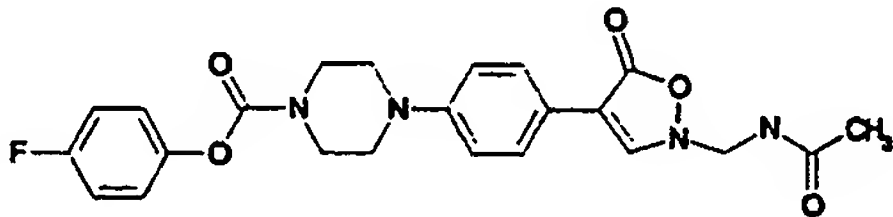
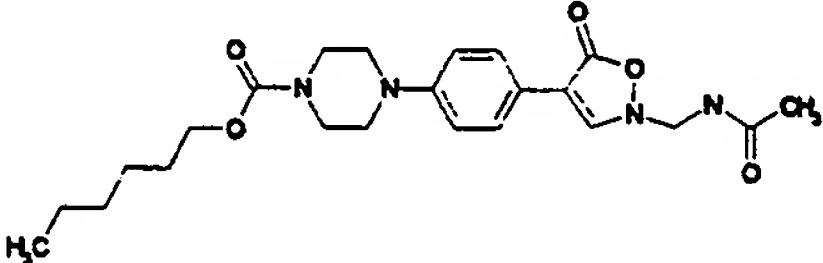
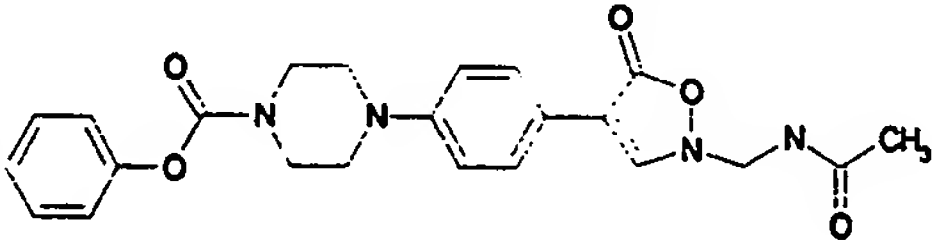
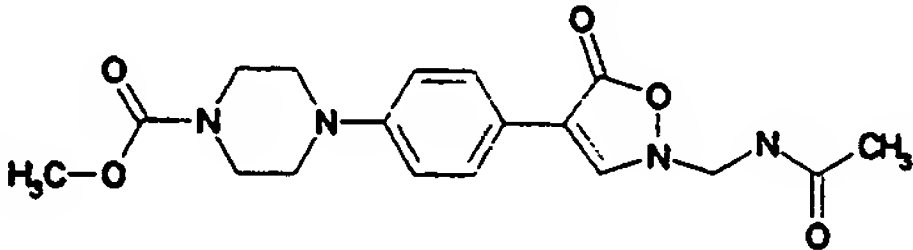
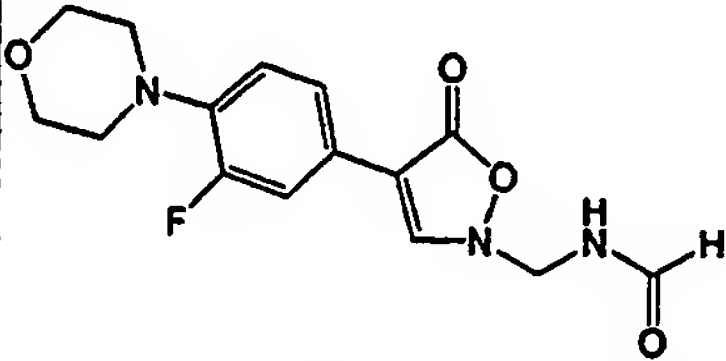
	Structure	MS data	Prepared via Scheme(s)
17		(M+H)+ = 358 ESI	1, 7
18		(M+H)+ = 342 DCI	1, 7
19		(M+H)+ = 325 DCI	1, 7
20		(M+H)+ = 248 DCI	1, 8
21		(M+H)+ = 326 DCI	1, 8
22		(M+H)+ = 298 ESI	1, 8
23		(M+H)+ = 341 ESI	1, 8
24		(M+H)+ = 417 ESI	2, 1, 6

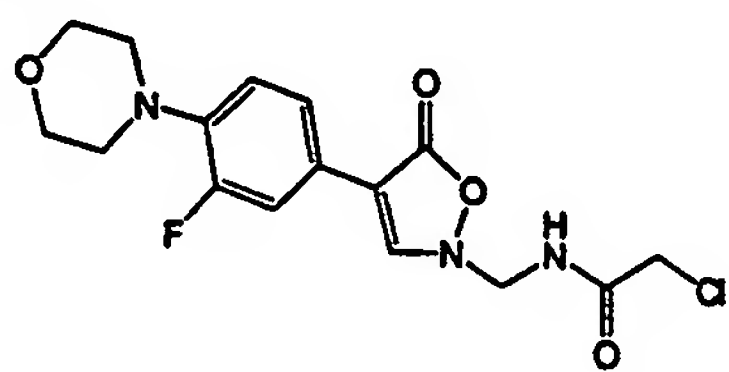
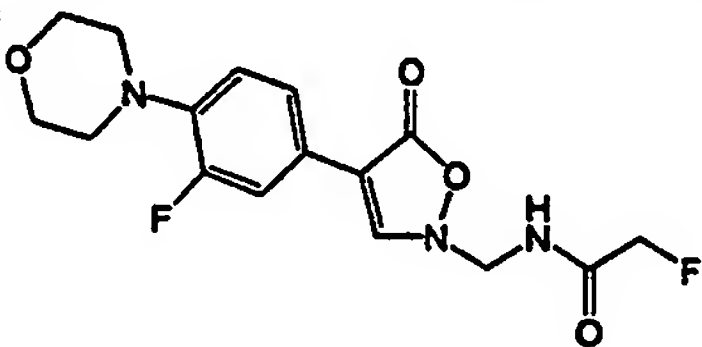
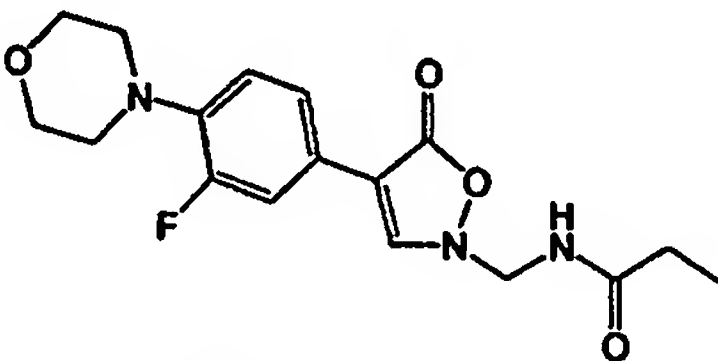
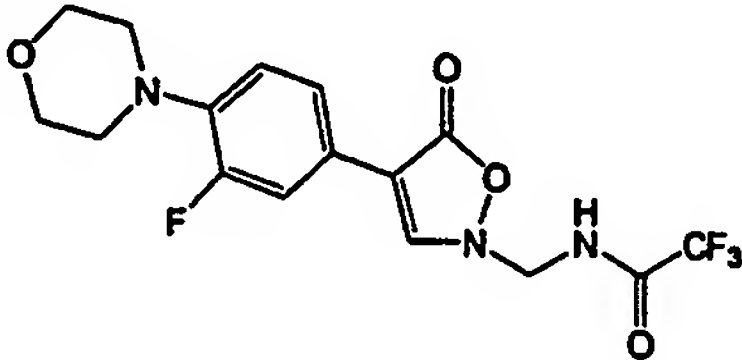
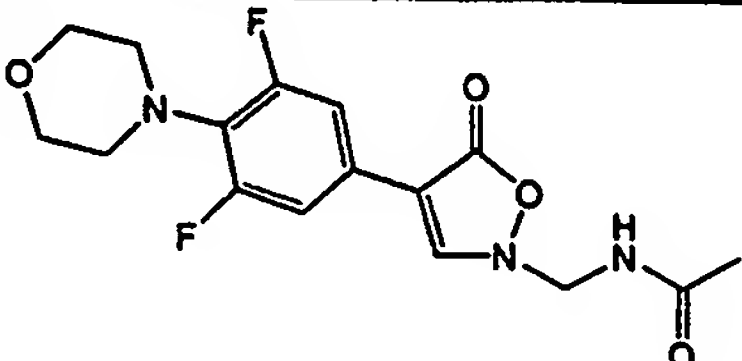
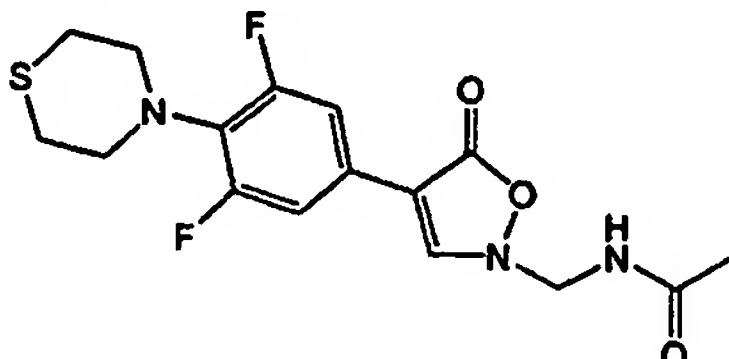
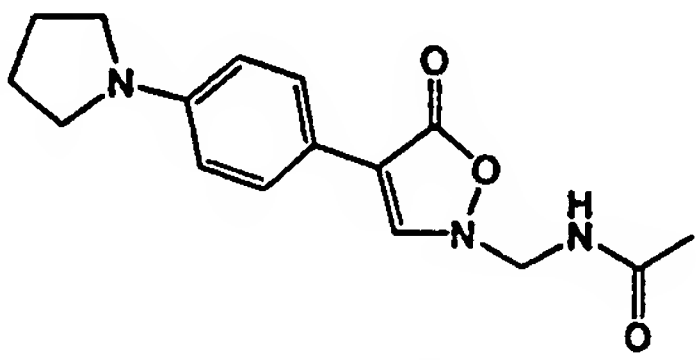
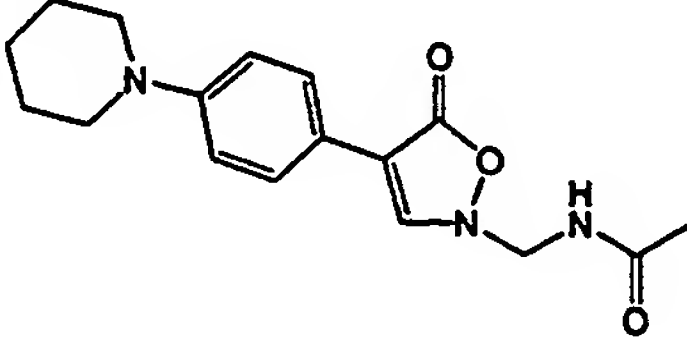
	Structure	MS data	Prepared via Scheme(s)
25		(M+H)+ = 317 ESI	2, 1, 6
26		(M+H)+ = 435 ESI	3, 1, 6
27		(M+H)+ = 318 ESI	2, 1
28		(M+H)+ = 334 ESI	3, 1
29		(M+H)+ = 297 DCI	3, 1
30		(M+H)+ = 281 ESI	3, 1
31		(M+H)+ = 295 ESI	3, 1
32		(M+H)+ = 323 ESI	1, 8

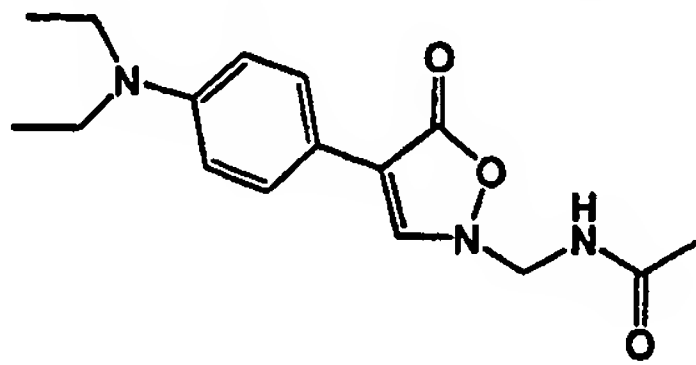
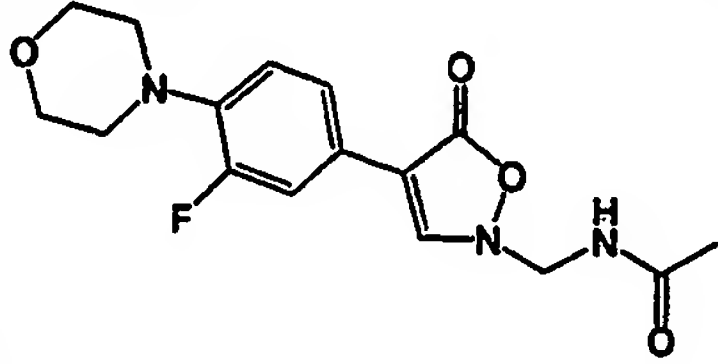
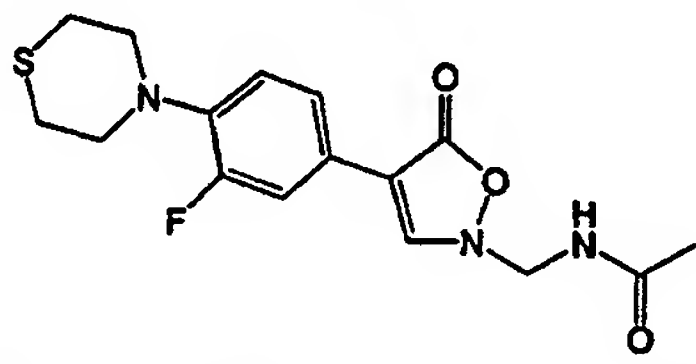
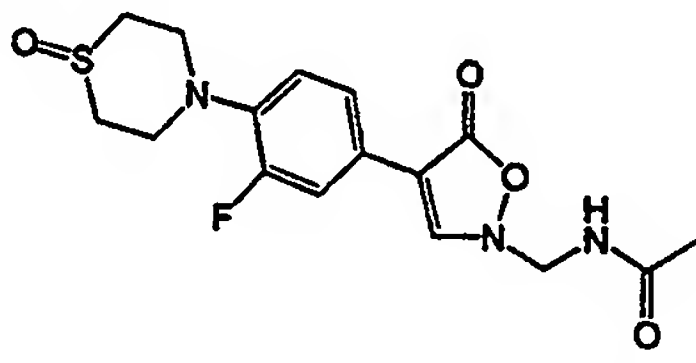
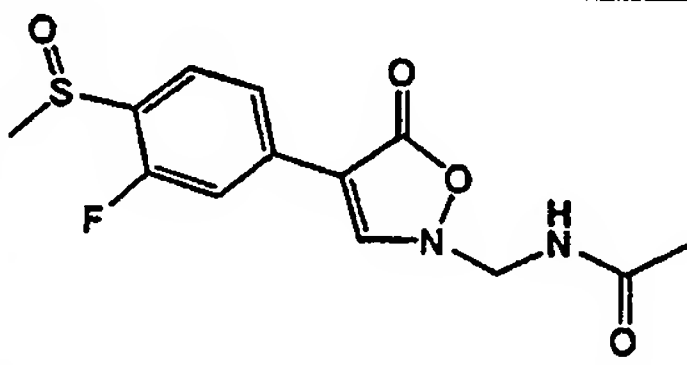
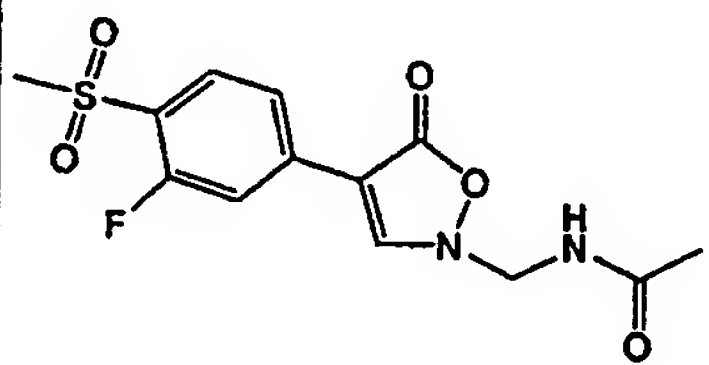
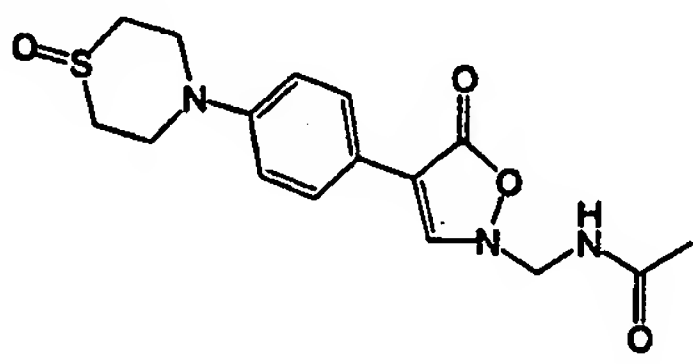
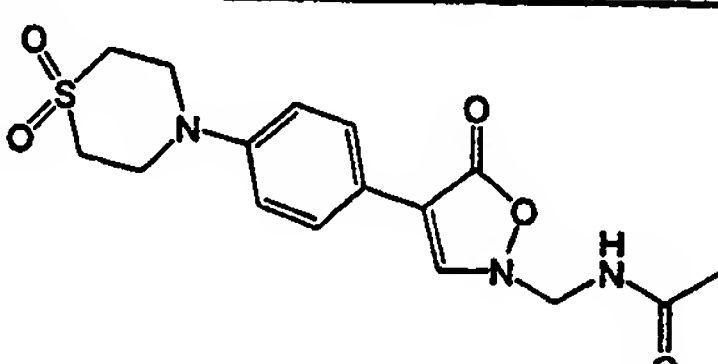
	Structure	MS data	Prepared via Scheme(s)
33		(M+H)+ = 324 DCI	1,8
34		(M+H)+ = 265 DCI	1
35		(M+H)+ = 313 DCI	1
36		(M+H)+ = 297 DCI	1
37		(M+H)+ = 281 ESI	1
38		(M+H)+ = 293 ESI	1
39		(M+H)+ = 309 ESI	1
40		(M+H)+ = 295 ESI	1

	Structure	MS data	Prepared via Scheme(s)
41		(M+H)+ = 369 DCI	1
42		(M+H)+ = 276 ESI	1
43		(M+H)+ = 299 ESI	1
44		(M+H)+ = 233 ESI	1
45		(M+H)+ = 309 ESI	1
46		(M+H)+ = 275 ESI	1
47		(M+H)+ = 359 ESI	1
48		(M+H)+ = 277 ESI	1

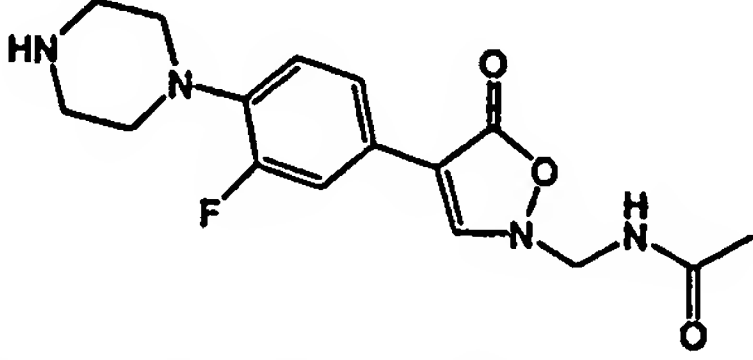
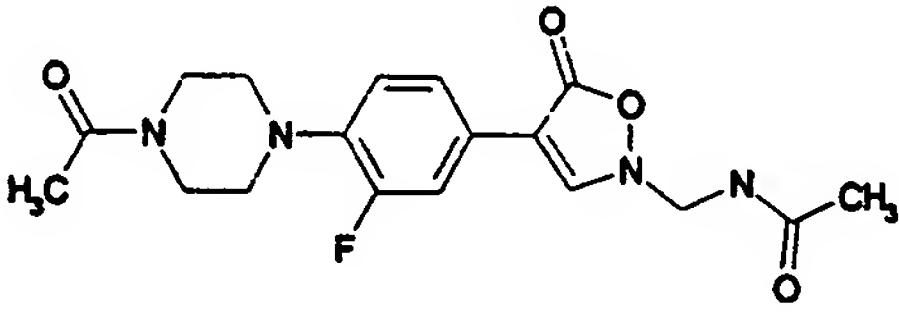
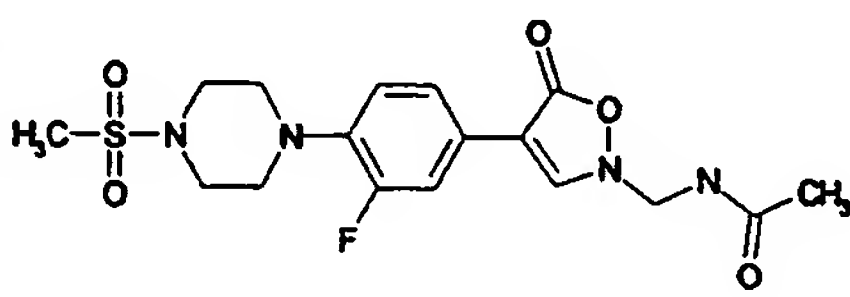
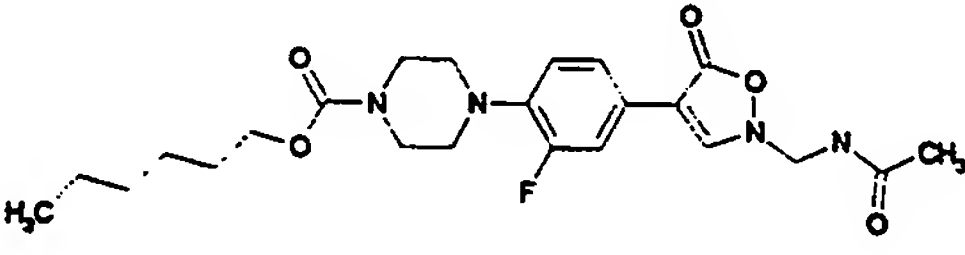
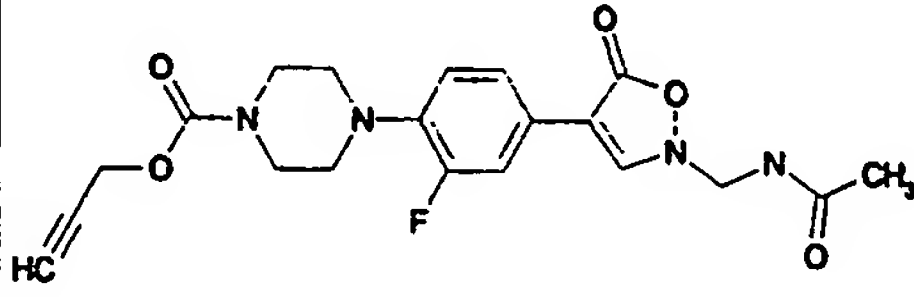
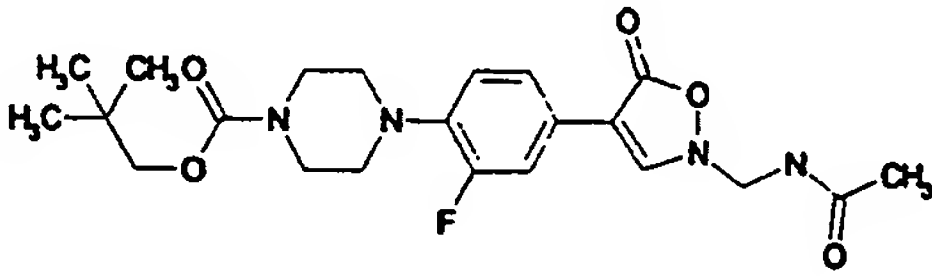
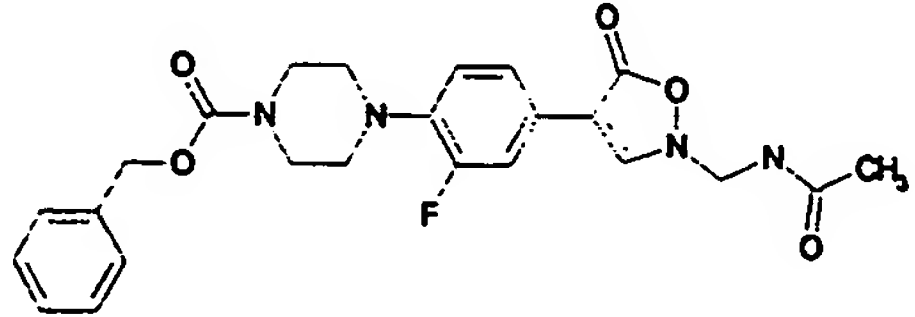
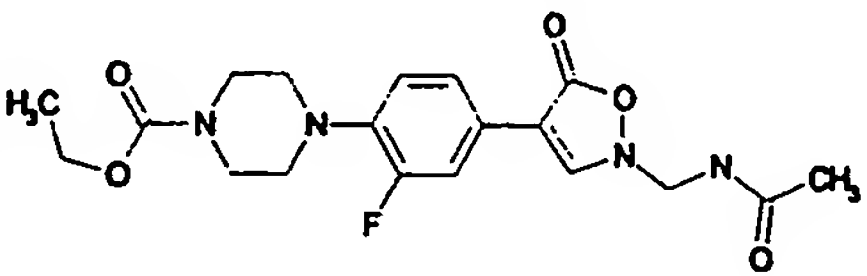
	Structure	MS data	Prepared via Scheme(s)
49		(M+H)+ = 309 ESI	1
50		(M+H)+ = 312 ESI	1
51		(M+H)+ = 268 ESI	1
52		(M+H)+ = 268 ESI	1
53		(M+H)+ = 251 ESI	1
54		(M+H)+ = 247 ESI	1
55		(M+H)+ = 277 ESI	1
56		(M+H)+ = 371 DCI	1,8

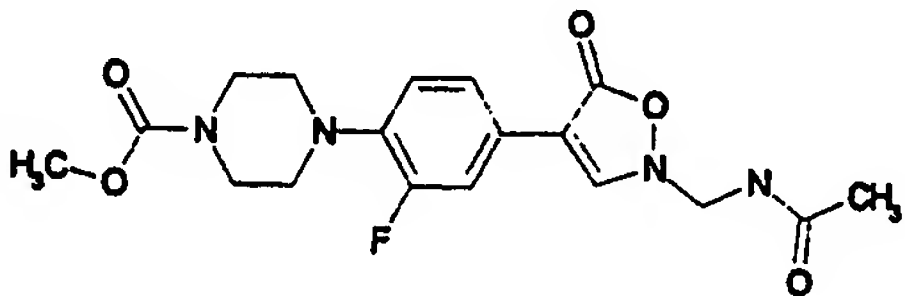
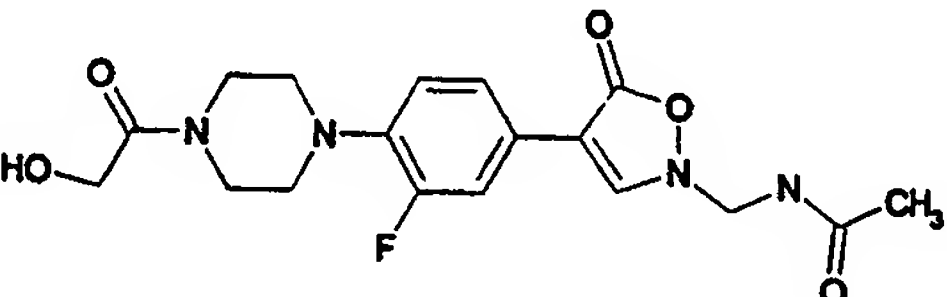
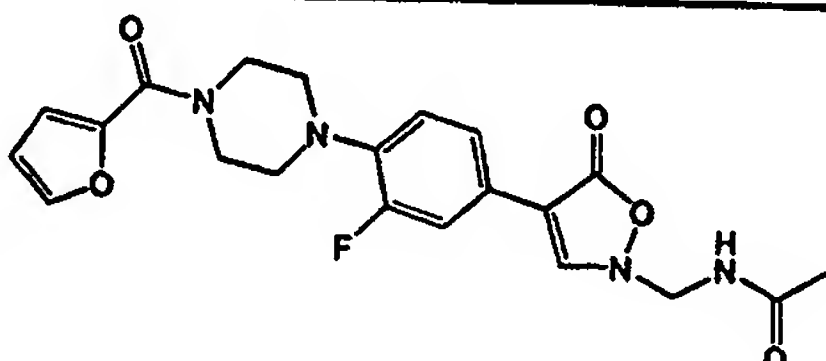
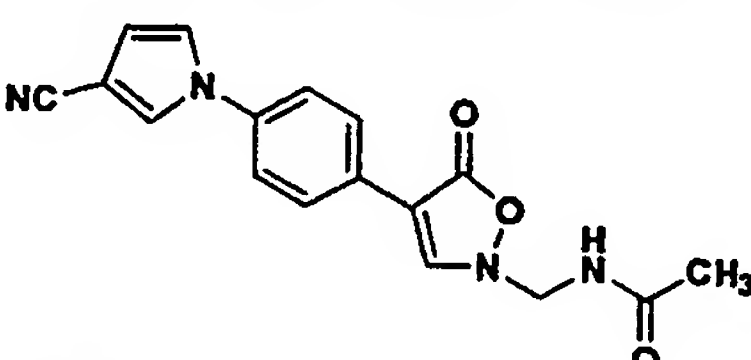
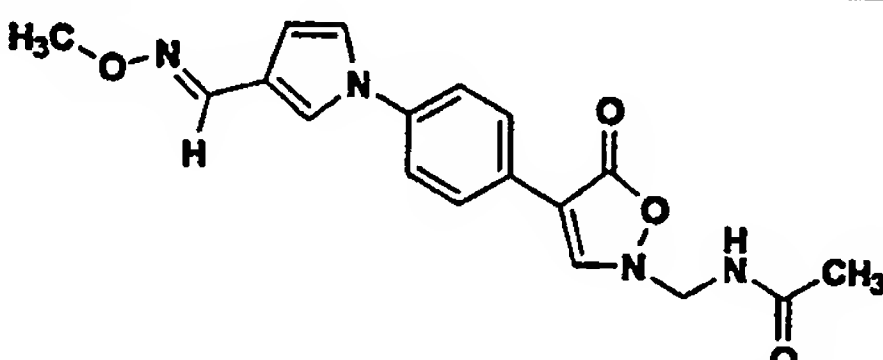
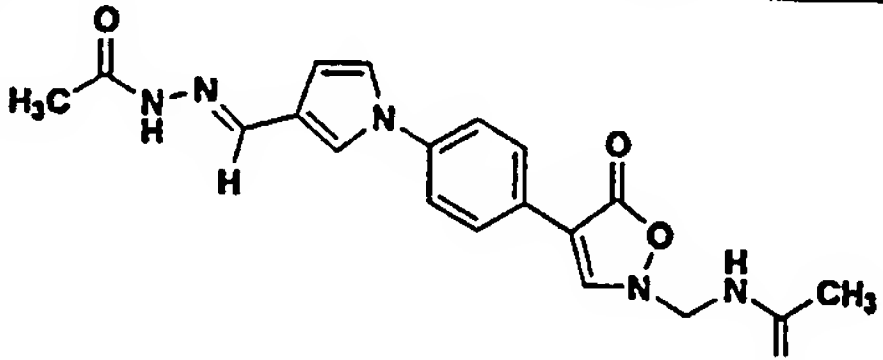
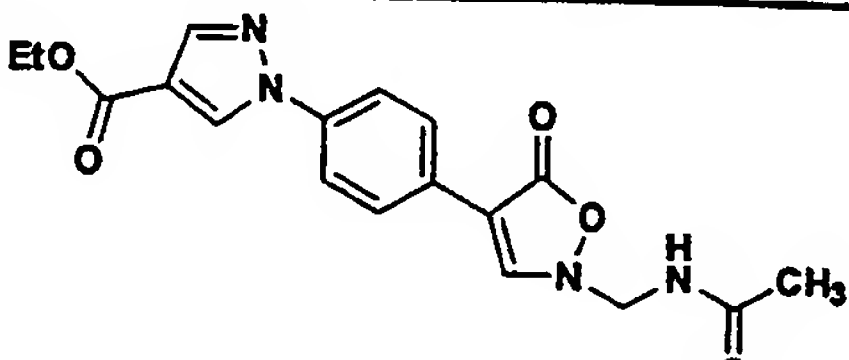
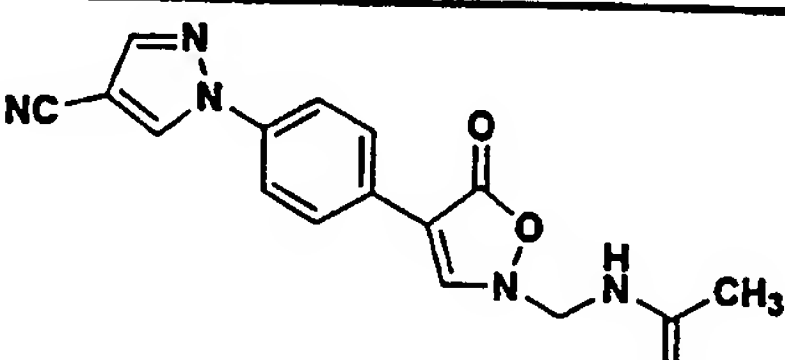
	Structure	MS data	Prepared via Scheme(s)
57		(M+H)+ = 395 ESI	2, 1, 6
58		(M+H)+ = 359 ESI	2, 1, 6
59		(M+H)+ = 399 ESI	2, 1, 6
60		(M+H)+ = 455 ESI	2, 1, 6
61		(M+H)+ = 445 ESI	2, 1, 6
62		(M+H)+ = 437 ESI	2, 1, 6
63		(M+H)+ = 375 ESI	2, 1, 6
64		(M+H)+ = 322 ESI	3, 1

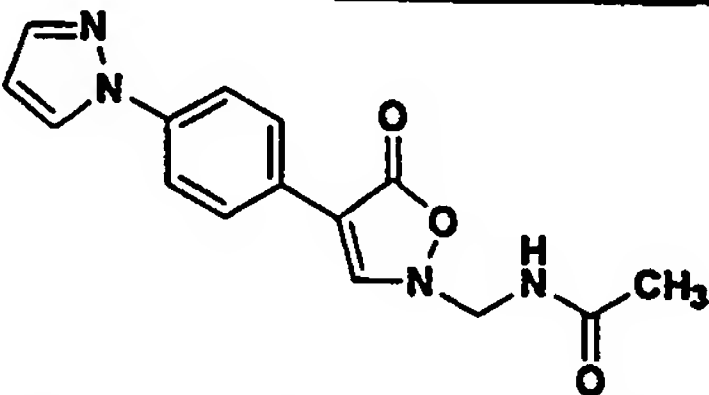
	Structure	MS data	Prepared via Scheme(s)
65		(M+H)+ = 370 ESI	3, 1
66		(M+H)+ = 354 ESI	3, 1
67		(M+H)+ = 350 ESI	3, 1
68		(M+H)+ = 390 ESI	3, 1
69		(M+H)+ = 354 ESI	3, 1
70		(M+H)+ = 370 ESI	3, 1
71		(M+H)+ = 302 ESI	3, 1
72		(M+H)+ = 316 ESI	3, 1

	Structure	MS data	Prepared via Scheme(s)
73		(M+H)+ = 304 ESI	3, 1
74		(M+H)+ = 336 ESI	3, 1
75		(M+H)+ = 352 ESI	3, 1
76		(M+H)+ = 368 ESI	3, 1, 4
77		(M+H)+ = 313 ESI	3, 1, 4
78		(M+H)+ = 329 ESI	3, 1, 4
79		(M+H)+ = 350 ESI	3, 1, 4
80		(M+H)+ = 366 ESI	3, 1, 4



	Structure	MS data	Prepared via Scheme(s)
81		(M+H)+ = 334 ESI	3, 1, 6
82		(M+H)+ = 377 ESI	3, 1, 6
83		(M+H)+ = 413 ESI	3, 1, 6
84		(M+H)+ = 463 ESI	3, 1, 6
85		(M+H)+ = 417 ESI	3, 1, 6
86		(M+H)+ = 449 ESI	3, 1, 6
87		(M+H)+ = 469 ESI	3, 1, 6
88		(M+H)+ = 407 ESI	3, 1, 6

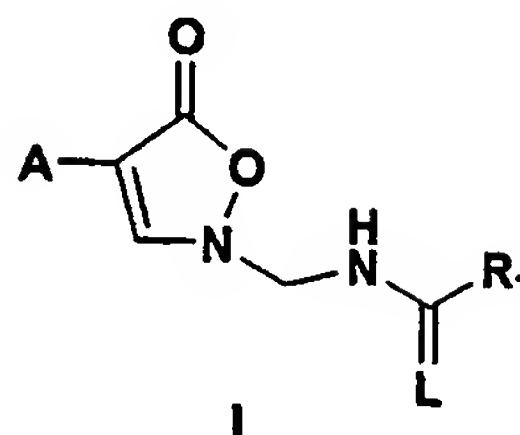
	Structure	MS data	Prepared via Scheme(s)
89		(M+H) <sup>+</sup> = 393 ESI	3, 1, 6
90		(M+H) <sup>+</sup> = 393 ESI	3, 1, 6
91		(M+H) <sup>+</sup> = 429 ESI	3, 1, 6
92		(M+H) <sup>+</sup> = 323 ESI	1, 8
93		(M+H) <sup>+</sup> = 355 ESI	1, 8
94		(M+H) <sup>+</sup> = 382 ESI	1, 8
95		(M+H) <sup>+</sup> = 371 DCI	1, 9
96		(M+H) <sup>+</sup> = 324 DCI	1, 9

	Structure	MS data	Prepared via Scheme(s)
97	 <chem>CN(C(=O)O[C@H]1C=C(C1c2ccc(cc2)N3C=CC=C3)C(=O)O)C</chem>	(M+H) <sup>+</sup> = 299 ESI	1, 9

CLAIMS

We claim:

- 5 1. A compound of the formula



or a pharmaceutically acceptable salt thereof wherein:

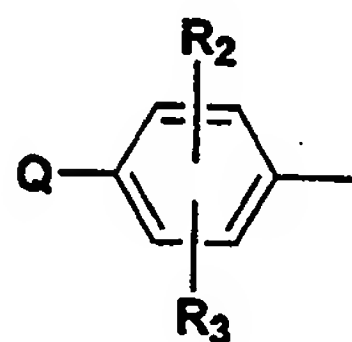
10  $R_1$  is

- a) H,
- b)  $C_{1-8}$  alkyl optionally substituted with one or more F, Cl, OH,  $C_{1-8}$  alkoxy, or  $C_{1-8}$  acyloxy,
- c)  $C_{3-6}$  cycloalkyl, or
- 15 d)  $C_{1-8}$  alkoxy;

L is oxygen or sulfur;

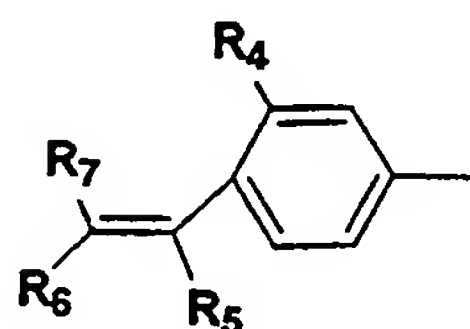
A is

a)



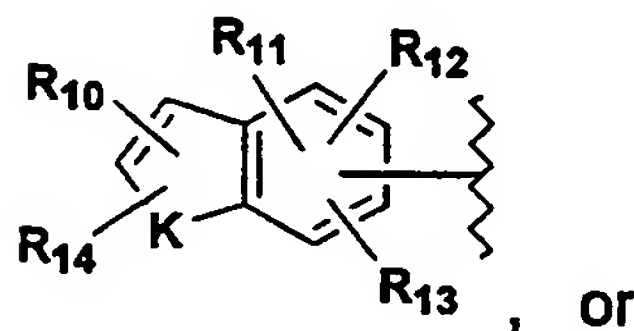
20

b)

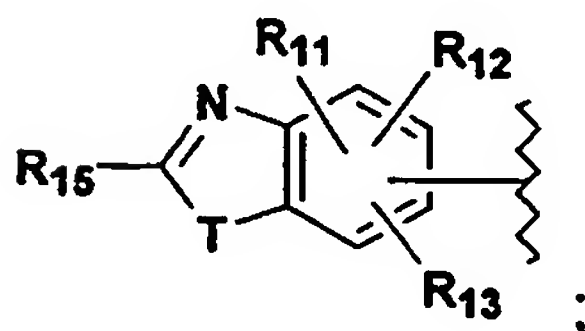


- 5 c) a 5-membered heteroaromatic moiety having one to three hetero atoms selected from the group consisting of S, N, and O, wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom and can additionally have a fused-on benzene or naphthyl ring, and wherein the heteroaromatic moiety is optionally substituted with one to three  $R_8$ ,
- 10 d) a 6-membered heteroaromatic moiety having at least one nitrogen atom, wherein the heteroaromatic moiety is bonded via a carbon atom, wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring, wherein the heteroaromatic moiety is optionally substituted with one to three  $R_9$ ,
- 15 e) a  $\beta$ -carbolin-3-yl, or indolizinyI bonded via the 6-membered ring, optionally substituted with one to three  $R_9$ ,

f)



g)



20 wherein  $R_2$  and  $R_3$  are each independently

- a) H,
- b) F,
- c) Cl,
- d) Br,
- 25 e)  $C_{1-6}$  alkyl,
- f)  $NO_2$ ,

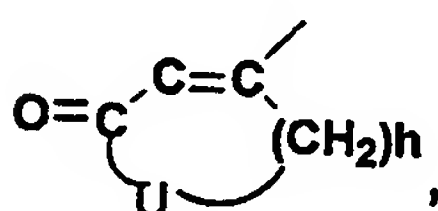
- 5
- g) I,
  - h) C<sub>1-6</sub> alkoxy,
  - i) OH
  - j) amino,
  - k) cyano, or
  - l) R<sub>2</sub> and R<sub>3</sub> taken together are -O(CH<sub>2</sub>)<sub>h</sub>-O;

wherein R<sub>4</sub> is

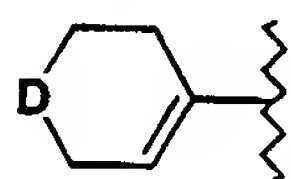
- 10
- a) H,
  - b) C<sub>1-2</sub> alkyl,
  - c) F, or
  - d) OH;

R<sub>5</sub> is

- 15
- a) H,
  - b) CF<sub>3</sub>,
  - c) C<sub>1-3</sub> alkyl optionally substituted with one or more halo,
  - d) phenyl optionally substituted with one or more halo,
  - e) R<sub>5</sub> and R<sub>6</sub> taken together are a 5-, 6-, or 7-membered ring of the formula,



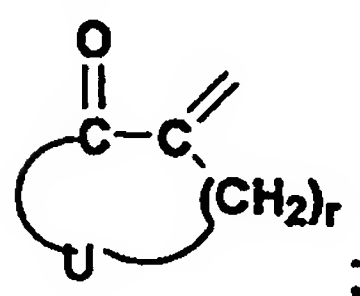
- 20
- f)



in which D is S, O or NR<sub>86</sub> in which R<sub>86</sub> is H or C<sub>1-6</sub> alkyl, or

- g) R<sub>5</sub> and R<sub>6</sub> taken together are -(CH<sub>2</sub>)<sub>k</sub>-, when R<sub>7</sub> is an electron-withdrawing group;
- 25 R<sub>6</sub> and R<sub>7</sub> at each occurrence are the same or different and are
- a) an electron-withdrawing group,
  - b) H,

- c)  $\text{CF}_3$ ,  
 d)  $\text{C}_{1-3}$  alkyl optionally substituted with one halo,  
 e) phenyl, provided at least one of  $\text{R}_6$  and  $\text{R}_7$  is an electron-withdrawing group, or  
 5 f)  $\text{R}_6$  and  $\text{R}_7$  taken together are a 5-, 6-, or 7-membered ring of the formula,



U is

- a)  $\text{CH}_2$ ,  
 10 b) O,  
 c) S or,  
 d)  $\text{NR}_{16}$ ;

$\text{R}_{16}$  is

- a) H or  
 15 b)  $\text{C}_{1-5}$  alkyl;

wherein  $\text{R}_8$  is

- a) carboxyl,  
 b) halo,  
 c)  $-\text{CN}$ ,  
 20 d) mercapto,  
 e) formyl,  
 f)  $\text{CF}_3$ ,  
 g)  $\text{NO}_2$ ,  
 h)  $\text{C}_{1-6}$  alkoxy,  
 25 i)  $\text{C}_{1-6}$  alkoxy carbonyl,  
 j)  $\text{C}_{1-6}$  alkythio,  
 k)  $\text{C}_{1-6}$  acyl,

l)  $-NR_{17}R_{18}$ ,

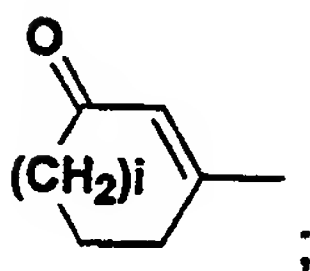
m)  $\begin{array}{c} \text{NOH} \\ \parallel \\ -\text{C}-\text{R}_{87} \end{array}$  in which  $R_{87}$  is H or  $C_{1-6}$  alkyl,

n)  $C_{1-6}$  alkyl optionally substituted with OH, sulfamoyl,  $C_{1-5}$  alkoxy,  $C_{1-5}$  acyl, or  $-NR_{17}R_{18}$ ,

5 o)  $C_{2-8}$  alkyl optionally substituted with one or two  $R_{19}$ ,

p) phenyl optionally substituted with one or two  $R_{19}$ ,

10 q) a 5- or 6-membered saturated or unsaturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two  $R_{19}$ , or



$R_{17}$  and  $R_{18}$  at each occurrence are the same or different and are

a) H,

b)  $C_{1-4}$  alkyl,

15 c)  $C_{5-6}$  cycloalkyl, or

20 d)  $R_{17}$  and  $R_{18}$  taken together with the nitrogen atom is a 5- or 6-membered saturated or unsaturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, O, and can in turn be optionally substituted with, including on the further nitrogen atom,  $C_{1-3}$  alkyl, formyl, a 5- or 6-membered heteroaromatic moiety

25 containing 1-3 O, N or S,  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{NR}_{88}\text{R}_{89} \end{array}$  in which  $R_{88}$  and  $R_{89}$  are each independently hydrogen or  $C_{1-6}$  alkyl,  $\text{SO}_2\text{R}_{90}$  in which  $R_{90}$  is H or  $C_{1-6}$  alkyl, or  $C_{1-3}$  acyl optionally substituted with 1 or more F, Cl or OH;



R<sub>19</sub> is

- a) carboxyl,
- b) halo,
- c) -CN,
- 5 d) mercapto,
- e) formyl,
- f) CF<sub>3</sub>,
- g) NO<sub>2</sub>,
- h) C<sub>1-6</sub> alkoxy,
- 10 i) C<sub>1-6</sub> alkoxy carbonyl,
- j) C<sub>1-6</sub> alkythio,
- k) C<sub>1-6</sub> acyl,
- l) C<sub>1-6</sub> alkyl optionally substituted with OH, C<sub>1-5</sub> alkoxy, C<sub>1-5</sub> acyl, or -NR<sub>17</sub>R<sub>18</sub>,
- 15 m) phenyl,
- n) -C(=O)NR<sub>20</sub>R<sub>21</sub>,
- o) -N R<sub>17</sub>R<sub>18</sub>,
- p) -N(R<sub>20</sub>)(-SO<sub>2</sub>R<sub>22</sub>),
- q) -SO<sub>2</sub>-NR<sub>20</sub>R<sub>21</sub>, or
- 20 r) -S(=O)<sub>i</sub>R<sub>22</sub>;

R<sub>20</sub> and R<sub>21</sub> at each occurrence are the same or different and are

- a) H,
- b) C<sub>1-6</sub> alkyl, or
- c) phenyl;

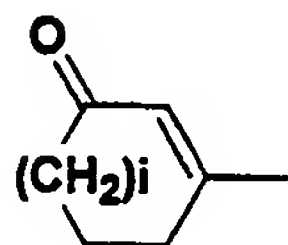
25 R<sub>22</sub> is

- a) C<sub>1-4</sub> alkyl, or
- b) phenyl optionally substituted with C<sub>1-4</sub> alkyl;

wherein  $R_9$  is

- 5
- a) carboxyl,
  - b) halo,
  - c) -CN,
  - d) mercapto,
  - e) formyl,
  - f)  $CF_3$ ,
  - g)  $NO_2$ ,
  - h)  $C_{1-6}$  alkoxy,
  - 10 i)  $C_{1-6}$  alkoxy carbonyl,
  - j)  $C_{1-6}$  alkythio,
  - k)  $C_{1-6}$  acyl,
  - l)  $-NR_{23}R_{24}$ ,
  - m)  $C_{1-6}$  alkyl optionally substituted with OH,  $C_{1-5}$  alkoxy,  $C_{1-5}$  acyl, or  $-NR_{23}R_{24}$ ,
  - 15 n)  $C_{2-8}$  alkenylphenyl optionally substituted with one or two  $R_{25}$ ,
  - o) phenyl optionally substituted with one or two  $R_{25}$ ,
  - p) a 5- or 6-membered saturated or unsaturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two  $R_{25}$ , or
  - 20

q)



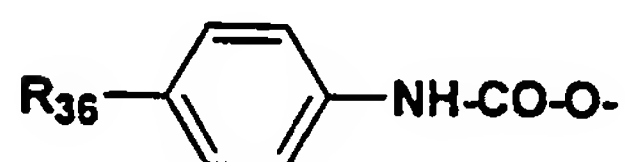
25  $R_{23}$  and  $R_{24}$  at each occurrence are the same or different and are

- a) H,
- b) formyl,

- 5
- c) C<sub>1-4</sub> alkyl,
  - d) C<sub>1-4</sub> acyl,
  - e) phenyl,
  - f) C<sub>3-6</sub> cycloalkyl, or
  - g) R<sub>23</sub> and R<sub>24</sub> taken together with the nitrogen atom is a 5- or 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, O, and can in turn be optionally substituted with, including on the further nitrogen atom,
- 10
- phenyl, pyrimidyl, C<sub>1-3</sub> alkyl, or C<sub>1-3</sub> acyl;

R<sub>25</sub> is

- a) carboxyl,
  - b) halo,
  - c) -CN,
  - 15 d) mercapto,
  - e) formyl,
  - f) CF<sub>3</sub>,
  - g) NO<sub>2</sub>,
  - h) C<sub>1-6</sub> alkoxy,
  - 20 i) C<sub>1-6</sub> alkoxy carbonyl,
  - j) C<sub>1-6</sub> alkythio,
  - k) C<sub>1-6</sub> acyl,
  - l) phenyl,
  - m) C<sub>1-6</sub> alkyl optionally substituted with OH, azido, C<sub>1-5</sub> alkoxy, C<sub>1-5</sub> acyl, -NR<sub>32</sub>R<sub>33</sub>, -SR<sub>34</sub>, -O-SO<sub>2</sub>R<sub>35</sub>, or
- 25



- n) -C(=O)NR<sub>26</sub>R<sub>27</sub>,
- o) -NR<sub>23</sub>R<sub>24</sub>,

- p)  $-N(R_{26})(-SO_2R_{22})$ ,  
q)  $-SO_2-NR_{26}R_{27}$ , or  
r)  $-S(=O)_iR_{22}$ ,  
s)  $-CH=N-R_{28}$ , or  
5 t)  $-CH(OH)-SO_3R_{31}$ ;

$R_{22}$  is the same as defined above;

$R_{26}$  and  $R_{27}$  at each occurrence are the same or different and are

- a) H,  
b)  $C_{1-6}$  alkyl,  
10 c) phenyl, or  
d) tolyl;

$R_{28}$  is

- a) OH,  
b) benzyloxy,  
15 c)  $-NH-C(=O)-NH_2$ ,  
d)  $-NH-C(=S)-NH_2$ , or  
e)  $-NH-C(=NH)-NR_{29}R_{30}$ ;

$R_{29}$  and  $R_{30}$  at each occurrence are the same or different and are

- a) H, or  
20 b)  $C_{1-4}$  alkyl optionally substituted with phenyl or pyridyl;

$R_{31}$  is

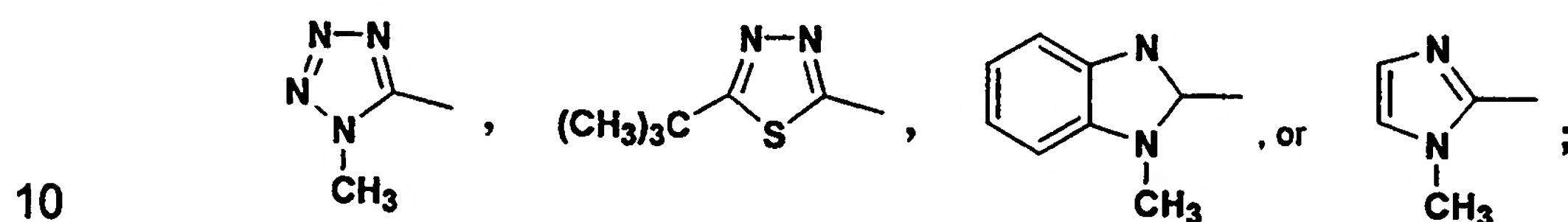
- a) H, or  
b) a sodium ion;

$R_{32}$  and  $R_{33}$  at each occurrence are the same or different and are

- 25 a) H,  
b) formyl,  
c)  $C_{1-4}$  alkyl,  
d)  $C_{1-4}$  acyl,  
e) phenyl,

- f) C<sub>3-6</sub> cycloalkyl,
- g) R<sub>32</sub> and R<sub>33</sub> taken together are a 5- or 6-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, O, optionally substituted with, including on the nitrogen atom, phenyl, pyrimidyl, C<sub>1-3</sub> alkyl, or C<sub>1-3</sub> acyl,
- h) -P(O)(OR<sub>37</sub>)(OR<sub>38</sub>), or
- i) -SO<sub>2</sub>-R<sub>39</sub>;

R<sub>34</sub> is



R<sub>35</sub> is C<sub>1-3</sub> alkyl;

R<sub>36</sub> is

- a) C<sub>1-6</sub> alkoxy carbonyl, or
- b) carboxyl;

15 R<sub>37</sub> and R<sub>38</sub> at each occurrence are the same or different and are

- a) H, or
- b) C<sub>1-3</sub> alkyl;

R<sub>39</sub> is

- 20 a) methyl,
- b) phenyl, or
- c) tolyl;

wherein K is

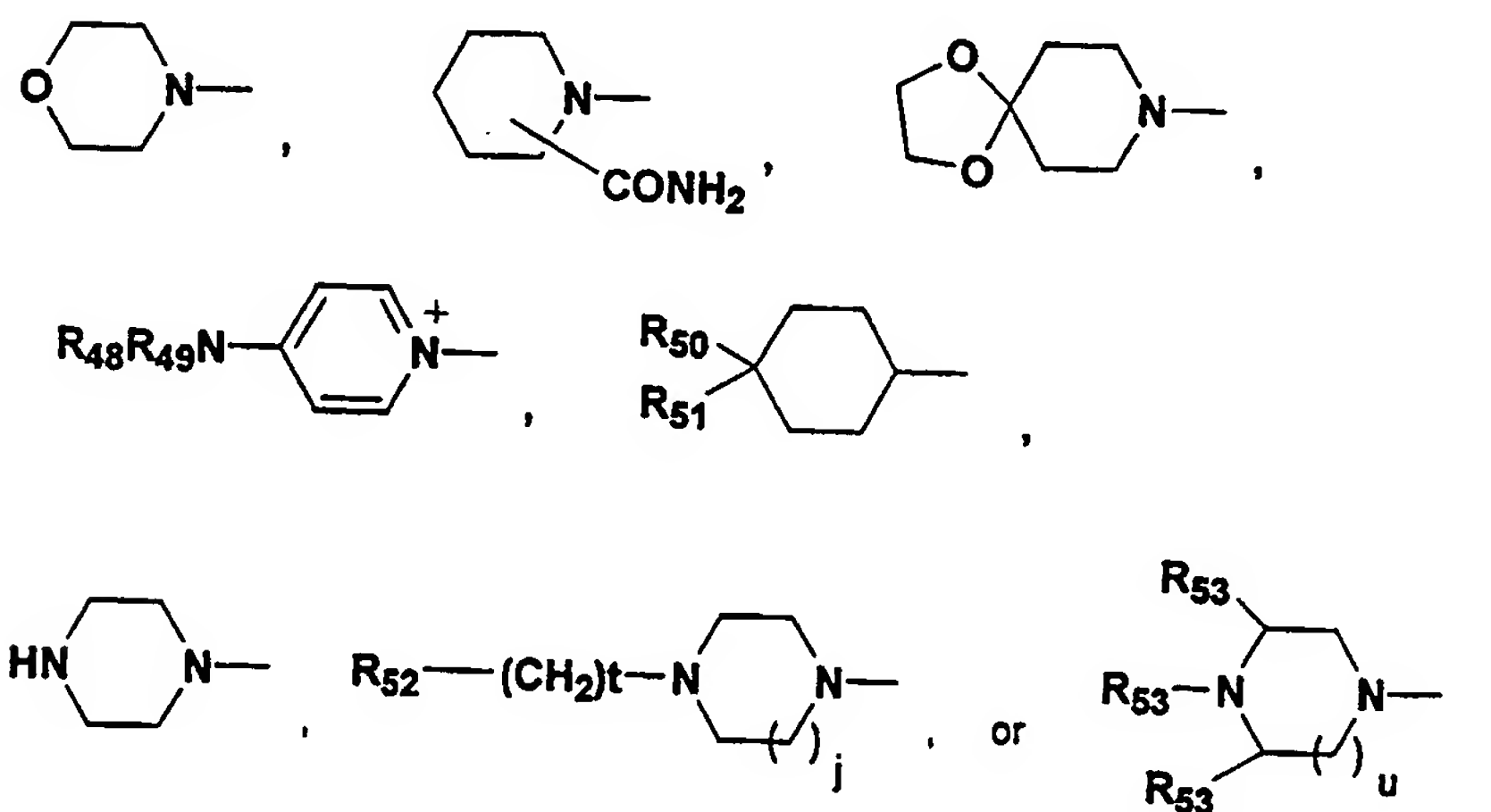
- a) O,
- b) S, or
- 25 c) NR<sub>40</sub> in which R<sub>40</sub> is hydrogen, formyl, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> acyl, phenyl, C<sub>3-6</sub> cycloalkyl, -P(O)(OR<sub>37</sub>)(OR<sub>38</sub>) or -SO<sub>2</sub>-R<sub>39</sub> in which R<sub>37</sub>, R<sub>38</sub> and R<sub>39</sub> are as defined above;

$R_{10}$ ,  $R_{11}$ ,  $R_{12}$ ,  $R_{13}$ ,  $R_{14}$  and  $R_{15}$  at each occurrence are the same or different and are

- 5
- a) H,
  - b) formyl,
  - c) carboxyl,
  - d)  $C_{1-6}$  alkoxy carbonyl,
  - e)  $C_{1-8}$  alkyl,
  - f)  $C_{2-8}$  alkenyl,

10 wherein the substituents (e) and (f) can be optionally substituted with OH, halo,  $C_{1-6}$  alkoxy,  $C_{1-6}$  acyl,  $C_{1-6}$  alkylthio or  $C_{1-6}$  alkoxy carbonyl, or phenyl optionally substituted with halo,

- 15
- g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl,  $CF_3$ ,  $NO_2$ ,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy,  $C_{1-6}$  acyl,  $C_{1-6}$  alkylthio, or  $C_{1-6}$  alkoxy carbonyl;
  - h)  $-NR_{42}R_{43}$ ,
  - i)  $OR_{44}$ ,
  - j)  $-S(=O)_i-R_{45}$ ,
  - k)  $-SO_2-N(R_{46})(R_{47})$ , or
  - 20 l) a radical of the following formulas:



$R_{19}$  is the same as defined above;

T is

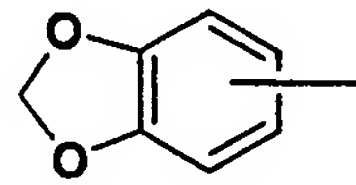
- a) O,
- b) S, or
- c) SO<sub>2</sub>;

5 R<sub>42</sub> and R<sub>43</sub> at each occurrence are the same or different and are

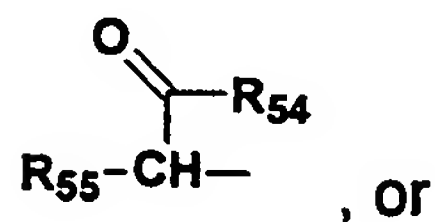
- a) H,
- b) C<sub>3-6</sub> cycloalkyl,
- c) phenyl,
- d) C<sub>1-6</sub> acyl,

10 e) C<sub>1-8</sub> alkyl optionally substituted with OH, C<sub>1-6</sub> alkoxy which can be substituted with OH, a 5- or 6-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, phenyl optionally substituted with OH, CF<sub>3</sub>, halo, -NO<sub>2</sub>, C<sub>1-4</sub>

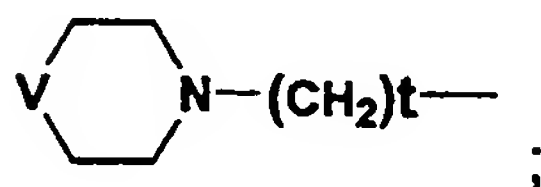
15 alkoxy, -NR<sub>48</sub>R<sub>49</sub>, or



f)



g)



20 V is

- a) O,
- b) CH<sub>2</sub>, or
- c) NR<sub>56</sub>;

R<sub>48</sub> and R<sub>49</sub> at each occurrence are the same or different and are

25 a) H, or  
b) C<sub>1-4</sub> alkyl;

R<sub>54</sub> is

- a) OH,
- b) C<sub>1-4</sub> alkoxy, or
- c) -NR<sub>57</sub>R<sub>58</sub>;

5 R<sub>55</sub> is

- a) H, or
- b) C<sub>1-7</sub> alkyl optionally substituted with indolyl, OH, mercaptyl, imidazolyl, methylthio, amino, phenyl optionally substituted with OH, -C(=O)-NH<sub>2</sub>, -CO<sub>2</sub>H, or -C(=NH)-NH<sub>2</sub>;

10 R<sub>56</sub> is

- a) H,
- b) phenyl, or
- c) C<sub>1-6</sub> alkyl optionally substituted by OH;

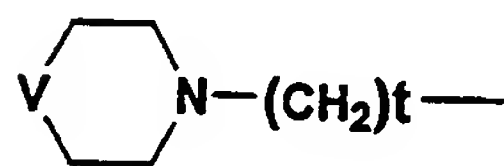
R<sub>57</sub> and R<sub>58</sub> at each occurrence are the same or different and are

- 15
- a) H,
  - b) C<sub>1-5</sub> alkyl,
  - c) C<sub>1-3</sub> cycloalkyl, or
  - d) phenyl;

R<sub>44</sub> is

- 20
- a) C<sub>1-8</sub> alkyl optionally substituted with C<sub>1-6</sub> alkoxy or C<sub>1-6</sub> hydroxy, C<sub>3-6</sub> cycloalkyl, a 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three nitrogen atoms, which can in turn be substituted with one or two -NO<sub>2</sub>, CF<sub>3</sub>, halo, -CN, OH, C<sub>1-5</sub> alkyl, C<sub>1-5</sub> alkoxy, or C<sub>1-5</sub> acyl,
- 25

b)



c) phenyl, or



d) pyridyl;

R<sub>45</sub> is

a) C<sub>1-16</sub> alkyl,

b) C<sub>2-16</sub> alkenyl,

5 wherein the substituents (a) and (b) can be optionally substituted with C<sub>1-6</sub> alkoxy carbonyl, or a 5-, 6-, or 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

c) an aromatic moiety having 6 to 10 carbon atoms, or

10 d) a 5-, 6-, or 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group of S, N, and O, wherein the substituents (c) and (d) can be optionally substituted with carboxyl, halo, -CN, formyl, CF<sub>3</sub>, -NO<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> acyl, C<sub>1-6</sub> alkylthio, or C<sub>1-6</sub> alkoxy carbonyl;

15 R<sub>46</sub> and R<sub>47</sub> at each occurrence are the same or different and are

a) H,

b) phenyl,

c) C<sub>1-6</sub> alkyl, or

20 d) benzyl;

R<sub>50</sub> and R<sub>51</sub> at each occurrence are the same or different and are

a) H,

b) OH,

25 c) C<sub>1-6</sub> alkyl optionally substituted with -NR<sub>48</sub>R<sub>49</sub> in which R<sub>48</sub> and R<sub>49</sub> are as defined above,

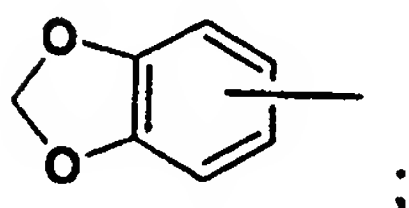
d) R<sub>50</sub> and R<sub>51</sub> taken together are =O;

R<sub>52</sub> is

a) an aromatic moiety having 6 to 10 carbon atoms,

5 b) a 5- or 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, wherein the substituents (a) and (b) can in turn be optionally substituted with one or three -NO<sub>2</sub>, CF<sub>3</sub>, halo, -CN, OH, phenyl, C<sub>1-5</sub> alkyl, C<sub>1-5</sub> alkoxy, or C<sub>1-5</sub> acyl,

- c) morpholinyl,  
 d) OH,  
 e) C<sub>1-6</sub> alkoxy,  
 10 f) -NR<sub>48</sub>R<sub>49</sub> in which R<sub>48</sub> and R<sub>49</sub> are as defined above,  
 g) -C(=O)-R<sub>59</sub>, or  
 h)



R<sub>53</sub> is

- 15 a) H,  
 b) formyl,  
 c) C<sub>1-4</sub> alkyl,  
 d) C<sub>1-4</sub> acyl,  
 e) phenyl,  
 20 f) C<sub>3-6</sub> cycloalkyl,  
 g) -P(O)(OR<sub>37</sub>)(OR<sub>38</sub>), or  
 h) -SO<sub>2</sub>R<sub>39</sub>, in which R<sub>37</sub>, R<sub>38</sub> and R<sub>39</sub> are as defined above;

R<sub>59</sub> is

- 25 a) morpholinyl,  
 b) OH, or  
 c) C<sub>1-6</sub> alkoxy;

h is 1, 2, or 3;

i is 0, 1, or 2;

j is 0, or 1;

k is 3, 4, or 5;

r is 1, 2, 3, 4, 5 or 6;

t is 0, 1, 2, 3, 4, 5, or 6;

5 u is 1 or 2; and

Q is

- a) hydrogen,
- b) halo,
- c) NO<sub>2</sub>,
- 10 d) N<sub>3</sub>,
- e) C<sub>1</sub>-C<sub>6</sub> alkylthio,
- f) C<sub>1</sub>-C<sub>6</sub> alkyl— $\overset{\text{O}}{\underset{\text{O}}{\text{S}}}$ —,
- g) C<sub>1</sub>-C<sub>6</sub> alkyl— $\overset{\text{O}}{\underset{\text{O}}{\underset{\text{O}}{\text{S}}}}$ —,
- h) C<sub>1</sub>-C<sub>6</sub> alkyl,
- 15 i) C<sub>1</sub>-C<sub>6</sub> alkoxy,
- j) formyl,
- k) C<sub>1</sub>-C<sub>6</sub> alkyl— $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$ —,
- l) C<sub>1</sub>-C<sub>6</sub> alkyl—O— $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$ —,
- m) -sulfamoyl (H<sub>2</sub>NSO<sub>2</sub>-),
- 20 n) -NHOH,
- o) C<sub>1</sub>-C<sub>6</sub> alkyl— $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$ -O—,
- p) heteroaryl — $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$ — in which heteroaryl is a 5- or 6-membered aromatic heterocyclic group having 1-3 hetero atoms selected from O, N or S,

- q)  $\text{C}_6\text{H}_5-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$ ,
- r) amino,
- s)  $\text{C}_1\text{-C}_6$  alkylamino,
- t) di( $\text{C}_1\text{-C}_6$  alkyl)amino-,
- 5 u)  $(\text{C}_1\text{-C}_6) \text{ alkyl}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{NR}_{60}\text{R}_{61}$  in which  $\text{R}_{60}$  and  $\text{R}_{61}$  are each independently hydrogen or  $\text{C}_1\text{-C}_6$  alkyl,
- v) OH,
- w) cyano,
- x) hydroxy ( $\text{C}_1\text{-C}_6$  alkyl),
- 10 y)  $\text{C}_1\text{-C}_6 \text{ alkyl}-\text{S}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$ ,
- z)  $\text{NC}-(\text{CH}_2)_r-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$  in which  $r$  is 1-6,
- aa)  $\text{C}_6\text{H}_5\text{CH}_2-\text{O}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$ ,
- bb)  $\text{C}_6\text{H}_5-\text{O}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$ ,
- cc)  $\text{C}_1\text{-C}_6 \text{ alkyl}-\overset{\text{N}-\text{OR}_{84}}{\underset{\parallel}{\text{C}}}-$  in which  $\text{R}_{84}$  is hydrogen or  $\text{C}_{1-6}$  alkyl,
- 15 dd)  $\text{R}_{85}\text{O}-(\text{CH}_2)_{1-6}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$  in which  $\text{R}_{85}$  is hydrogen,  $\text{C}_{1-8}$  alkyl optionally substituted with one or more F, Cl, OH,  $\text{C}_{1-8}$  alkoxy or  $\text{C}_{1-8}$  acyloxy,  $\text{C}_{3-6}$  cycloalkyl or  $\text{C}_{1-8}$  alkoxy;
- ee)  $\text{H}-\overset{\text{N}-\text{OR}_{84}}{\underset{\parallel}{\text{C}}}-$  in which  $\text{R}_{84}$  is hydrogen or  $\text{C}_{1-6}$  alkyl,
- ff) a substituted or unsubstituted  $\text{C}_6\text{-C}_{10}$  aryl moiety,
- 20 gg) a substituted or unsubstituted monocyclic or bicyclic, saturated or unsaturated, heterocyclic moiety having 1-3

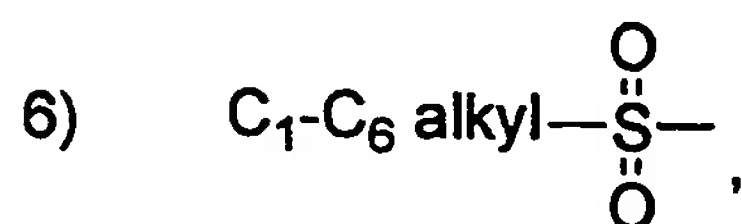
atoms selected from O, N or S, said ring being bonded via a ring carbon or nitrogen to the phenyl substituent,

- hh) a monocyclic or bicyclic substituted or unsubstituted heteroaromatic moiety having 1-3 hetero atoms selected from O, N or S, said ring being bonded via a ring carbon or nitrogen to the phenyl substituent and wherein the heteroaromatic moiety can additionally have a fused-on benzene or naphthalene ring;

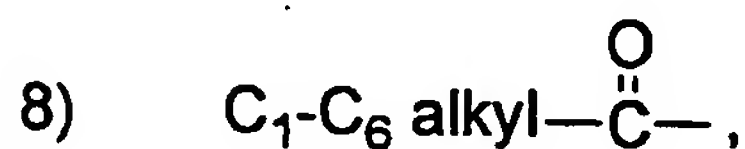
the substituents for such p, q, ff, gg and hh moieties being selected from

1 or 2 of the following:

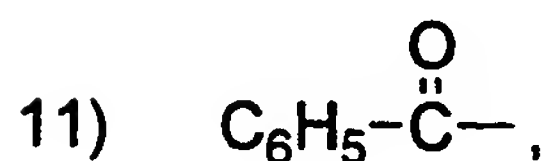
- 1) halo,
- 2) C<sub>1-6</sub> alkyl,
- 3) NO<sub>2</sub>,
- 4) N<sub>3</sub>,



- 7) formyl,

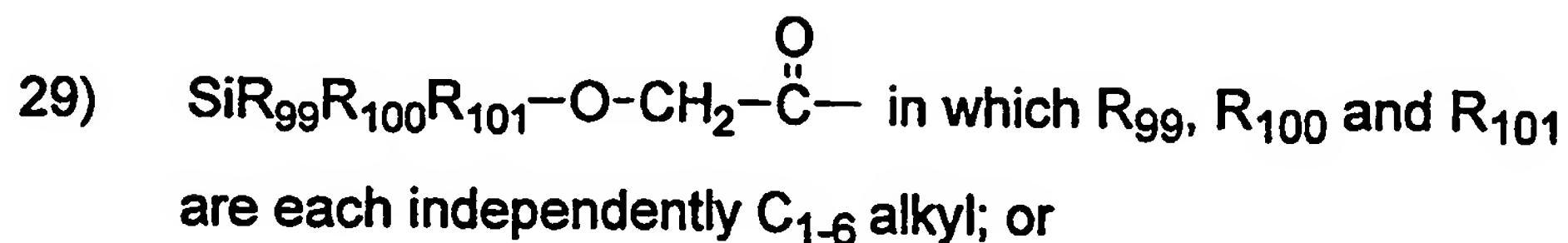
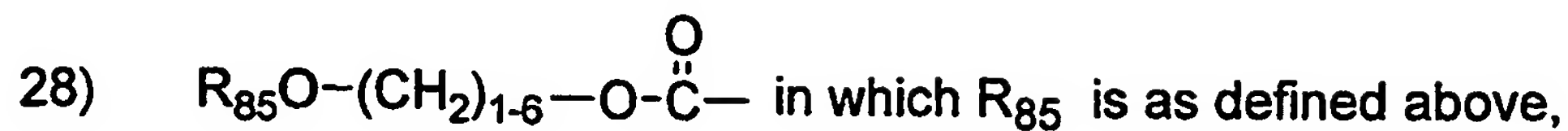
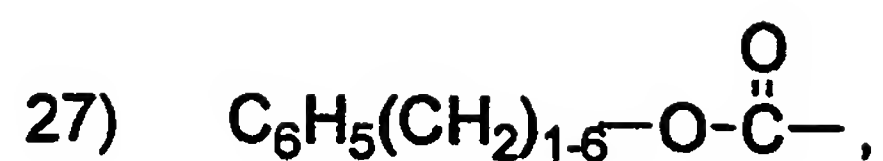


- 10) heteroaryl —  $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}—$  in which heteroaryl is a 5- or 6-membered aromatic heterocyclic group having 1-3 hetero atoms selected from O, N or S,



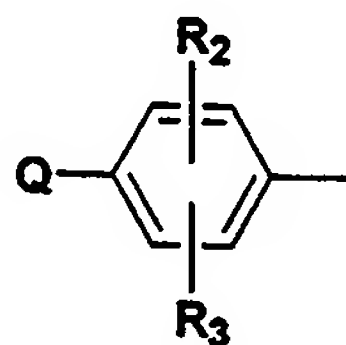
- 12) —(C<sub>1</sub>-C<sub>6</sub>) alkyl —  $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}—\text{NR}_{60}\text{R}_{61}$  in which R<sub>60</sub> and R<sub>61</sub> are each independently hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl,

- 13) OH,
- 14) hydroxy (C<sub>1</sub>-C<sub>6</sub> alkyl),
- 15) C<sub>1</sub>-C<sub>6</sub> alkyl—S— $\overset{\text{O}}{\overset{\parallel}{\text{C}}}$ —,
- 16) NC—(CH<sub>2</sub>)<sub>r</sub>—O— $\overset{\text{O}}{\overset{\parallel}{\text{C}}}$ — in which r is 1-6,
- 5 17) C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>—O— $\overset{\text{O}}{\overset{\parallel}{\text{C}}}$ —,
- 18) -CH<sub>2</sub>-R<sub>80</sub> in which R<sub>80</sub> is
- a) -OR<sub>32</sub> in which R<sub>32</sub> is as defined above,
- b) -SR<sub>32</sub> in which R<sub>32</sub> is as defined above,
- c) -NR<sub>32</sub>R<sub>33</sub> in which R<sub>32</sub> and R<sub>33</sub> are as defined
- 10 above, or
- d) 5- or 6-membered heteroaromatic containing 1-4 O,  
S or N atoms,
- 19) C<sub>1</sub>-C<sub>6</sub> alkyl— $\overset{\text{N}}{\overset{\parallel}{\text{C}}}$ — $\overset{\text{OR}_{84}}{\text{N}}$  in which R<sub>84</sub> is as defined above,
- 20) cyano,
- 15 21) carboxyl,
- 22) CF<sub>3</sub>,
- 23) C<sub>1</sub>-C<sub>6</sub> alkyl— $\overset{\text{O}}{\overset{\parallel}{\text{C}}}$ -O—,
- 24) C<sub>6</sub>H<sub>5</sub>-O— $\overset{\text{O}}{\overset{\parallel}{\text{C}}}$ — in which the phenyl moiety may be optionally  
substituted by halo or (C<sub>1</sub>-C<sub>6</sub>)alkyl,
- 20 25) NR<sub>60</sub>R<sub>61</sub>— $\overset{\text{O}}{\overset{\parallel}{\text{C}}}$ — in which R<sub>60</sub> and R<sub>61</sub> are as defined above,
- 26) R<sub>91</sub>-NH— $\overset{\text{O}}{\overset{\parallel}{\text{C}}}$ — or R<sub>91</sub>— $\overset{\text{O}}{\overset{\parallel}{\text{C}}}$ -NH— in which R<sub>91</sub> is a 5- or 6-  
membered aromatic heterocyclic group having 1-3 O, N or  
S,



5 Q and either  $\text{R}_1$  and  $\text{R}_2$  taken together form  $-\text{O}-\text{CH}_2-\text{O}-$ .

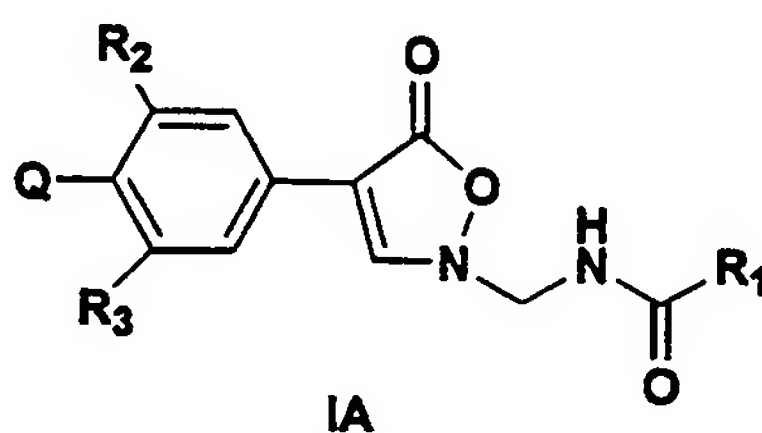
2. A compound of claim 1 wherein A is



10

in which  $\text{Q}$ ,  $\text{R}_2$  and  $\text{R}_3$  are as defined in claim 1.

3. A compound of the formula



15

or a pharmaceutically acceptable salt thereof, in which

$\text{R}_1$  is H,  $\text{C}_{1-8}$  alkyl optionally substituted with one or more F, Cl, OH,  $\text{C}_{1-8}$  alkoxy, or  $\text{C}_{1-8}$  acyloxy,  $\text{C}_{3-6}$  cycloalkyl or  $\text{C}_{1-8}$  alkoxy;

20

$\text{R}_2$  and  $\text{R}_3$  are each independently

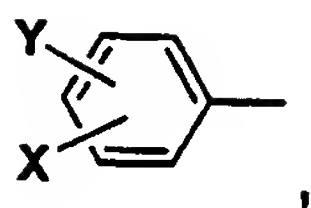
a) H,

- 5
- b) F,
  - c) Cl,
  - d) Br,
  - e) C<sub>1-6</sub> alkyl,
  - f) NO<sub>2</sub>,
  - g) I,
  - h) C<sub>1-6</sub> alkoxy,
  - i) OH
  - j) amino, or
  - 10 k) cyano; and
- Q is
- a) hydrogen,
  - b) halo,
  - c) NO<sub>2</sub>,
  - 15 d) N<sub>3</sub>,
  - e) C<sub>1-C6</sub> alkylthio,
  - f) C<sub>1-C6</sub> alkyl —  $\overset{\text{O}}{\underset{\text{O}}{\text{S}}} —$ ,
  - g) C<sub>1-C6</sub> alkyl —  $\overset{\text{O}}{\underset{\text{O}}{\text{S}}} —$ ,
  - h) C<sub>1-C6</sub> alkyl,
  - 20 i) C<sub>1-C6</sub> alkoxy,
  - j) formyl,
  - k) C<sub>1-C6</sub> alkyl —  $\overset{\text{O}}{\text{C}} —$ ,
  - l) C<sub>1-C6</sub> alkyl —  $\text{O} — \overset{\text{O}}{\text{C}} —$ ,
  - m) C<sub>1-C6</sub> alkyl —  $\overset{\text{O}}{\text{C}} — \text{O} —$ ,

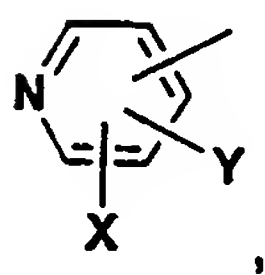


- 5
- n) heteroaryl— $\overset{\text{O}}{\underset{\parallel}{\text{C}}}$ — in which heteroaryl is a 5- or 6-membered aromatic heterocyclic group having 1-3 hetero atoms selected from O, N or S,
- o)  $\text{C}_6\text{H}_5\text{—}\overset{\text{O}}{\underset{\parallel}{\text{C}}}\text{—}$ ,
- p) amino,
- q)  $\text{C}_1\text{—C}_6$  alkylamino-,
- r) di( $\text{C}_1\text{—C}_6$  alkyl)amino-,
- 10
- s) ( $\text{C}_1\text{—C}_6$ ) alkyl— $\overset{\text{O}}{\underset{\parallel}{\text{C}}}$ — $\text{NR}_{60}\text{R}_{61}$ , in which  $\text{R}_{60}$  and  $\text{R}_{61}$  are each independently hydrogen or  $\text{C}_1\text{—C}_6$  alkyl,
- t) OH,
- u) cyano,
- v) hydroxy ( $\text{C}_1\text{—C}_6$  alkyl),
- w)  $\text{C}_1\text{—C}_6$  alkyl— $\text{S—}\overset{\text{O}}{\underset{\parallel}{\text{C}}}\text{—}$ ,
- x)  $\text{NC—(CH}_2\text{)}_r\text{—O—}\overset{\text{O}}{\underset{\parallel}{\text{C}}}\text{—}$  in which r is 1-6,
- 15
- y)  $\text{C}_6\text{H}_5\text{CH}_2\text{—O—}\overset{\text{O}}{\underset{\parallel}{\text{C}}}\text{—}$ ,
- z)  $\text{C}_6\text{H}_5\text{—O—}\overset{\text{O}}{\underset{\parallel}{\text{C}}}\text{—}$ ,
- aa)  $\text{C}_1\text{—C}_6$  alkyl— $\overset{\text{N—OR}_{84}}{\underset{\parallel}{\text{C}}}\text{—}$  wherein  $\text{R}_{84}$  is hydrogen or  $\text{C}_{1-6}$  alkyl,
- bb)  $\text{R}_{85}\text{O—(CH}_2\text{)}_{1-6}\text{—}\overset{\text{O}}{\underset{\parallel}{\text{C}}}\text{—}$  in which  $\text{R}_{85}$  is hydrogen,  $\text{C}_{1-8}$  alkyl, optionally substituted with one or more F, Cl, OH,  $\text{C}_{1-8}$  alkoxy or  $\text{C}_{1-8}$  acyloxy,  $\text{C}_{3-6}$  cycloalkyl or  $\text{C}_{1-8}$  alkoxy,
- 20
- cc)  $\text{H—}\overset{\text{N—OR}_{84}}{\underset{\parallel}{\text{C}}}\text{—}$  in which  $\text{R}_{84}$  is as defined above,

dd)

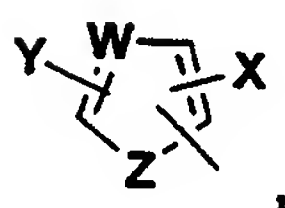


ee)

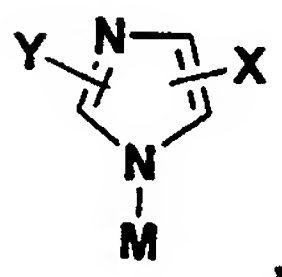


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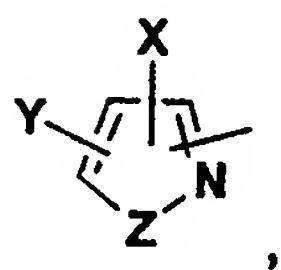
ff)



gg)

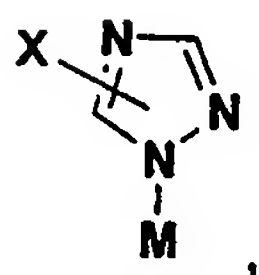


hh)

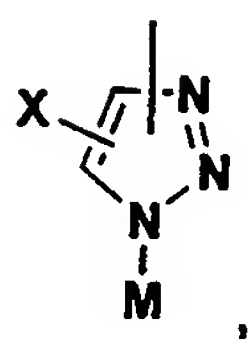


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ii)

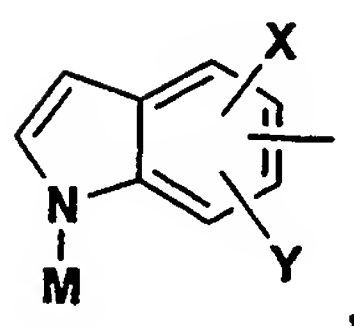


jj)

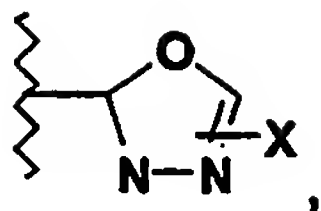


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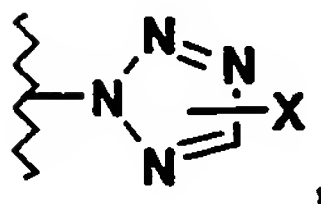
kk)



ll)

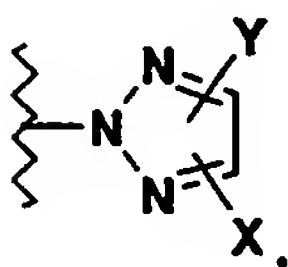


mm)

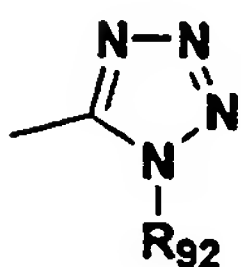


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nn)

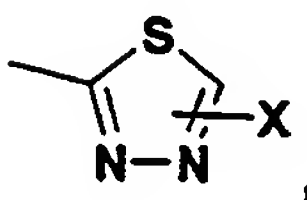


oo)



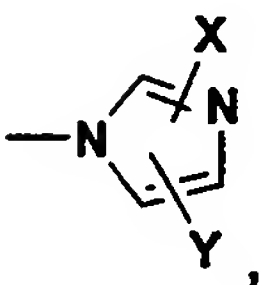
in which  $R_{92}$  is H or  $C_{1-6}$  alkyl,

pp)

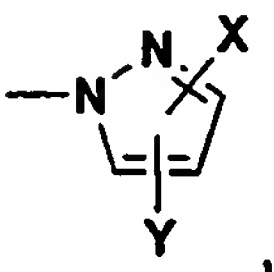


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qq)

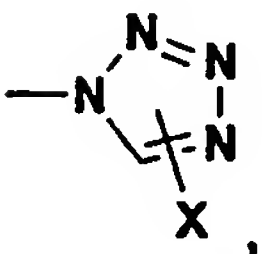


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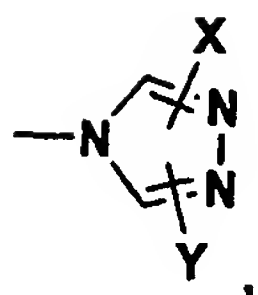


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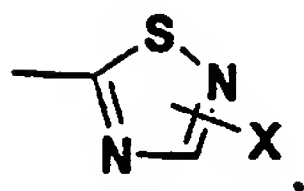
ss)



tt)

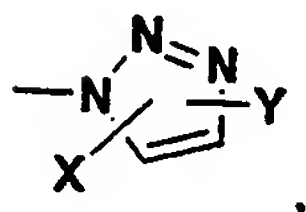


uu)

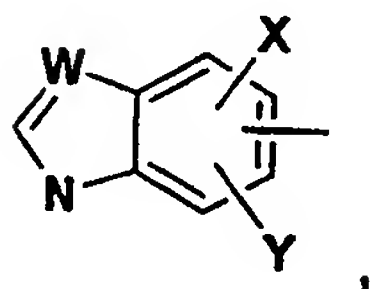


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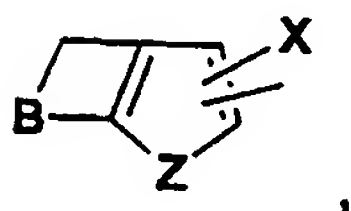
vv)



ww)

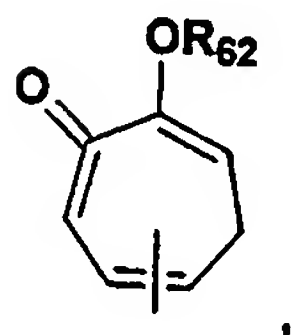


xx)

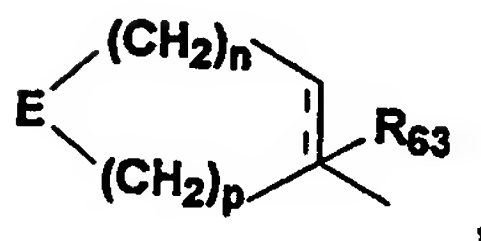


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yy)



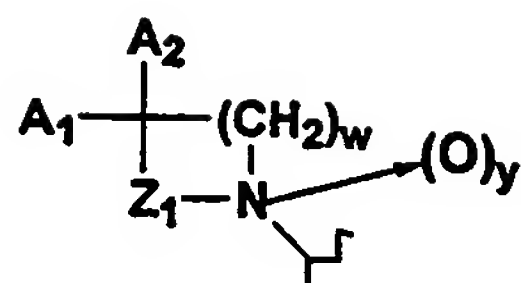
zz)



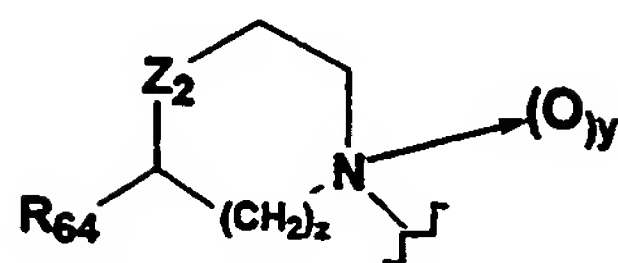
15

- aaa) a diazinyl group optionally substituted with X and Y,
- bbb) a triazinyl group optionally substituted with X and Y,
- ccc) a quinoliny group optionally substituted with X and Y,
- ddd) a quinoxaliny group optionally substituted with X and Y,
- eee) a naphthyridiny group optionally substituted with X and Y,

fff)

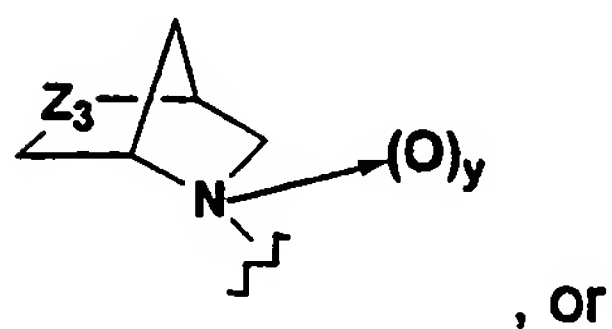


ggg)



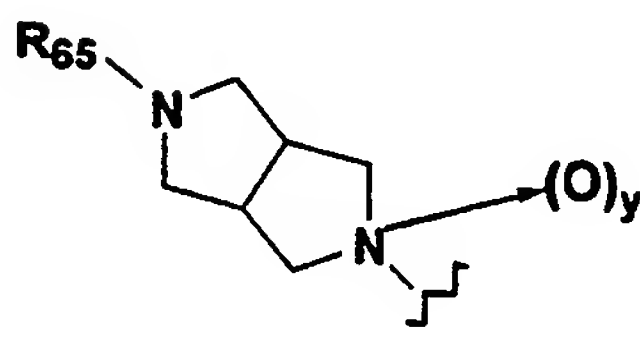
5

hhh)



, or

iii)



;

B is an unsaturated 4-atom linker having one nitrogen and three carbons;

10 M is

- a) H,
- b) C<sub>1-8</sub> alkyl,
- c) C<sub>3-8</sub> cycloalkyl,
- d) -(CH<sub>2</sub>)<sub>m</sub>OR<sub>66</sub>, or
- 15 e) -(CH<sub>2</sub>)<sub>n</sub>NR<sub>67</sub>R<sub>68</sub>;

Z is

- a) O,
- b) S or
- c) NM;

20 W is

- a) CH,
- b) N or

c) S or O when Z is NM;

X and Y are each independently

5 a) hydrogen,

b) halo,

c) NO<sub>2</sub>,

d) N<sub>3</sub>,

e) C<sub>1-6</sub> alkythio,

f) C<sub>1-6</sub> alkyl— $\overset{\text{O}}{\underset{\text{O}}{\text{S}}}$ —,

g) C<sub>1-6</sub> alkyl— $\overset{\text{O}}{\underset{\text{O}}{\underset{\text{O}}{\text{S}}}}$ —,

10 h) C<sub>1-6</sub> alkyl,

i) C<sub>1-6</sub> alkoxy,

j) formyl,

k) C<sub>1-6</sub> alkyl— $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$ —,

l) C<sub>1-6</sub> alkyl—O— $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$ —,

15 m) heteroaryl— $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$ — in which heteroaryl is a 5- or 6-membered aromatic heterocyclic group having 1-3 hetero atoms selected from O, N or S,

n) C<sub>6</sub>H<sub>5</sub>— $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$ —,

o) amino,

20 p) C<sub>1-6</sub> alkylamino-,

q) di (C<sub>1-6</sub> alkyl)amino-,

- 5
- r)  $-(C_1-C_6) \text{ alkyl}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-\text{NR}_{60}\text{R}_{61}$  in which  $\text{R}_{60}$  and  $\text{R}_{61}$  are each independently hydrogen or  $\text{C}_1-C_6$  alkyl,
- s) OH,
- t) hydroxy ( $\text{C}_1-C_6$  alkyl),
- u)  $\text{C}_1-C_6 \text{ alkyl}-\text{S}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-$ ,
- v)  $\text{NC}-(\text{CH}_2)_r-\text{O}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-$  in which  $r$  is 1-6,
- w)  $\text{C}_6\text{H}_5\text{CH}_2-\text{O}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-$ ,
- x)  $\text{C}_6\text{H}_5-\text{O}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-$ ,
- 10 y)  $\text{C}_1-C_6 \text{ alkyl}-\overset{\text{N}-\text{OR}_{84}}{\overset{\parallel}{\text{C}}}-$  in which  $\text{R}_{84}$  is as defined above,
- z) cyano,
- aa) carboxyl,
- bb)  $\text{CF}_3$ ,
- cc) mercapto,
- dd)  $\text{C}_1-C_6 \text{ alkyl}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-\text{O}-$ ,
- 15 ee)  $\text{C}_6\text{H}_5-\text{O}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-$  in which the phenyl moiety may be optionally substituted by halo or  $\text{C}_1-C_6$  alkyl,
- ff)  $\text{C}_6\text{H}_5(\text{CH}_2)_{1-6}-\text{O}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-$ ,
- gg)  $\text{R}_{85}\text{O}-(\text{CH}_2)_{1-6}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-$  in which  $\text{R}_{85}$  is as defined above, or
- hh)  $\text{SiR}_{99}\text{R}_{100}\text{R}_{101}-\text{O}-\text{CH}_2-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-$  in which  $\text{R}_{99}$ ,  $\text{R}_{100}$  and  $\text{R}_{101}$  are each independently  $\text{C}_{1-6}$  alkyl; or
- 20

Q and either  $\text{R}_1$  and  $\text{R}_3$  taken together form  $-\text{O}-\text{CH}_2-\text{O}-$ ;

R<sub>62</sub> is

- 5
- a) H,
  - b) C<sub>1-8</sub> alkyl optionally substituted with one or more halos, or
  - c) C<sub>1-8</sub> alkyl optionally substituted with one or more OH, or  
C<sub>1-8</sub> alkoxy;

E is

- a) NR<sub>69</sub>,
- b) -S(=O)<sub>i</sub> in which i is 0, 1 or 2, or
- c) O;

10 R<sub>63</sub> is

- a) H,
- b) C<sub>1-6</sub> alkyl,
- c) -(CH<sub>2</sub>)<sub>q</sub>-aryl, or
- d) halo;

15 R<sub>66</sub> is H or C<sub>1-4</sub> alkyl;

R<sub>67</sub> and R<sub>68</sub> are each independently H or C<sub>1-4</sub> alkyl, or NR<sub>67</sub>R<sub>68</sub> taken together are -(CH<sub>2</sub>)<sub>m</sub>;

R<sub>69</sub> is

- 20
- a) H,
  - b) C<sub>1-6</sub> alkyl,
  - c) -(CH<sub>2</sub>)<sub>q</sub>-aryl,
  - d) -CO<sub>2</sub>R<sub>81</sub>,
  - e) COR<sub>82</sub>,
  - f) -C(=O)-(CH<sub>2</sub>)<sub>q</sub>-C(=O)R<sub>81</sub>,
  - 25 g) -S(=O)<sub>z</sub>-C<sub>1-6</sub> alkyl,
  - h) -S(=O)<sub>z</sub>-(CH<sub>2</sub>)<sub>q</sub>-aryl, or
  - i) -(C=O)<sub>j</sub>-Het in which j is 0 or 1;



$Z_1$  is

- a)  $-\text{CH}_2-$ , or
- b)  $-\text{CH}(\text{R}_{70})-\text{CH}_2-$ ;

$Z_2$  is

- 5 a)  $-\text{O}_2\text{S}-$ ,
- b)  $-\text{O}-$ ,
- c)  $-\text{S}-$ ,
- d)  $-\text{SO}-$ , or
- e)  $-\text{N}(\text{R}_{71})-$ ;

10  $Z_3$  is

- a) S,
- b) SO,
- c)  $\text{SO}_2$ , or
- d) O;

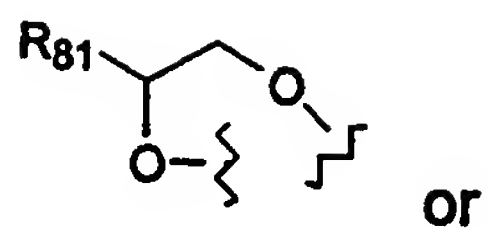
15  $A_1$  is H or  $\text{CH}_3$ ;

$A_2$  is

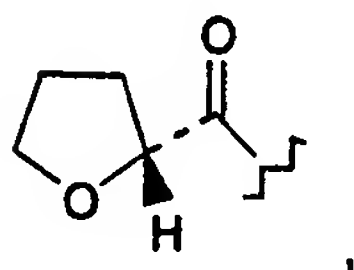
- a) H,
- b)  $\text{OH}-$ ,
- c)  $\text{CH}_3\text{CO}_2-$ ,
- 20 d)  $\text{CH}_3-$ ,
- e)  $\text{CH}_3\text{O}-$ ,
- f)  $\text{R}_{72}\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$ ,
- g)  $\text{R}_{73}\text{O}-\text{C}(\text{O})-\text{NH}-$ ,
- h)  $\text{R}_{73}-\text{C}(\text{O})-\text{NH}-$ ,
- 25 i)  $(\text{C}_1-\text{C}_2)\text{alkyl}-\text{O}-\text{C}(\text{O})-$ , or
- j)  $\text{HO}-\text{CH}_2$ ; or

$A_1$  and  $A_2$  taken together are

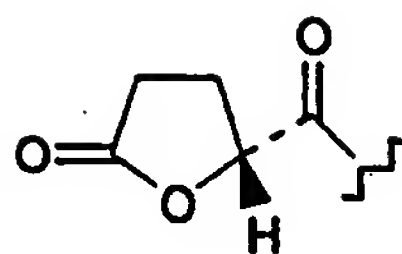
a)

b)  $O =$  ; $R_{64}$  is H or  $CH_3-$ ;5  $m$  is 4 or 5; $n$  is 0, 1, 2, 3, 4 or 5; $y$  is 0 or 1; $p$  is 0, 1, 2, 3, 4 or 5; $w$  is 1, 2 or 3;10  $q$  is 1, 2, 3 or 4; $z$  is 0 or 1; $R_{65}$  isa)  $R_{74}OC(R_{75})(R_{76})-C(O)-$ ,b)  $R_{77}OC(O)-$ ,15 c)  $R_{78}(O)-$ ,d)  $R_{79}-SO_2-$ , ore)  $R_{80}-NH-C(O)-$ ; $R_{70}$  is H or  $(C_1-C_3)$ alkyl; $R_{71}$  is20 a)  $R_{74}OC(R_{75})(R_{76})-C(O)-$ ,b)  $R_{77}O-C(O)-$ ,c)  $R_{78}-C(O)-$ ,

d)

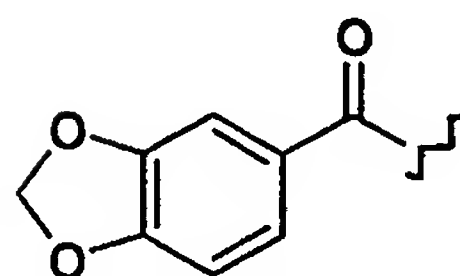


e)

f)  $\text{H}_3\text{C}-\text{C}(\text{O})-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,g)  $\text{R}_{79}-\text{SO}_2-$ ,

5

h)

i)  $\text{R}_{80}-\text{NH}-\text{C}(\text{O})-$ , $\text{R}_{72}$  is

- 10
- a) H,
  - b)  $\text{CH}_3$ ,
  - c) phenyl- $\text{CH}_2-$ , or
  - d)  $\text{CH}_3\text{C}(\text{O})-$ ;

 $\text{R}_{73}$  is  $(\text{C}_1-\text{C}_3)$ alkyl or phenyl; $\text{R}_{74}$  is H,  $\text{CH}_3$ , phenyl- $\text{CH}_2-$  or  $\text{CH}_3-\text{C}(\text{O})-$ ;

- 15
- $\text{R}_{75}$  and  $\text{R}_{76}$  are each independently H or  $\text{CH}_3$ , or  $\text{R}_{75}$  and  $\text{R}_{76}$  taken together are  $-\text{CH}_2\text{CH}_2-$ ;

 $\text{R}_{77}$  is  $(\text{C}_1-\text{C}_3)$ alkyl or phenyl;

$\text{R}_{78}$  is H,  $(\text{C}_1-\text{C}_4)$ alkyl, aryl- $(\text{CH}_2)_{n1}$ ,  $\text{ClH}_2\text{C}$ ,  $\text{Cl}_2\text{HC}$ ,  $\text{FH}_2\text{C}-$ ,  $\text{F}_2\text{HC}-$  or  $(\text{C}_3-\text{C}_6)$ cycloalkyl;

- 20
- $\text{R}_{79}$  is  $\text{CH}_3$ ;  $-\text{CH}_2\text{Cl}$ ,  $-\text{CH}_2\text{CH}=\text{CH}_2$ , aryl or  $-\text{CH}_2\text{CN}$ ;

 $\text{R}_{80}$  is  $-(\text{CH}_2)_{n1}$ -aryl where  $n^1$  is 0 or 1; $\text{R}_{81}$  is

- a) H,

- b)  $C_{1-6}$  alkyl optionally substituted with one or more OH, halo or CN,
- c)  $-(CH_2)_q$ -aryl in which q is as defined above, or
- d)  $-(CH_2)_q$ -OR<sub>83</sub> in which q is as defined above;

5 R<sub>82</sub> is

- a)  $C_{1-6}$  alkyl optionally substituted with one or more OH, halo or CN,
- b)  $-(CH_2)_q$ -aryl in which q is as defined above, or
- c)  $-(CH_2)_q$ -OR<sub>83</sub> in which q is as defined above;

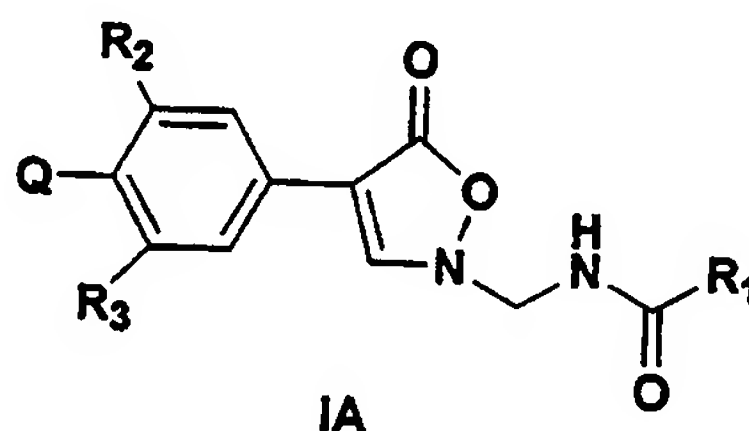
10 R<sub>83</sub> is

- a) H,
- b)  $C_{1-6}$  alkyl,
- c)  $-(CH_2)_q$ -aryl in which q is as defined above; or
- d)  $-C(=O)$   $C_{1-6}$  alkyl; and

15 aryl is phenyl, pyridyl or naphthyl, said phenyl, pyridyl or naphthyl moieties being optionally substituted by one or more halo, -CN, OH, SH,  $C_{1-6}$  alkoxy or  $C_{1-6}$  alkylthio.

4. A compound of the formula

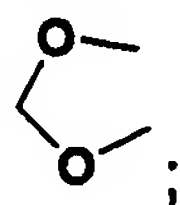
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or a pharmaceutically acceptable salt thereof, in which

25 R<sub>1</sub> is H,  $C_{1-8}$  alkyl optionally substituted with one or more F, Cl, OH,  $C_{1-8}$  alkoxy or  $C_{1-8}$  acyloxy,  $C_{3-6}$  cycloalkyl or  $C_{1-8}$  alkoxy;

$R_2$  and  $R_3$  are each independently H or F; or  $R_2$  and  $R_3$  taken together represent



$Q$  is

- 5
  - a) hydrogen,
  - b) halo,
  - c)  $N_3$ ,
  - d)  $NO_2$ ,
  - e)  $C_1$ - $C_6$  alkylthio,
- 10
  - f)  $C_1$ - $C_6$  alkyl— $\overset{\overset{O}{\parallel}}{S}$ —,
  - g)  $C_1$ - $C_6$  alkyl— $\overset{\overset{O}{\parallel}}{\underset{\underset{O}{\parallel}}{S}}$ —,
  - h)  $C_1$ - $C_6$  alkyl,
  - i)  $C_1$ - $C_6$  alkoxy,
  - j) formyl,
- 15
  - k)  $C_1$ - $C_6$  alkyl— $\overset{\overset{O}{\parallel}}{C}$ —,
  - l)  $C_1$ - $C_6$  alkyl—O— $\overset{\overset{O}{\parallel}}{C}$ —,
  - m)  $C_1$ - $C_6$  alkyl— $\overset{\overset{O}{\parallel}}{C}$ -O—,
  - n)  $(C_1$ - $C_6$  alkoxy) $_2N$ —,
  - o) 5- or 6-membered heterocyclic containing 1-3 O, N or S and
- 20
  - linked to the phenyl substituent via a carbon or nitrogen,
  - said heterocycle moiety being optionally substituted by  $R_{96}$ ,
  - p)  $C_1$ - $C_6$  alkyl— $\overset{\overset{N(OH)}{\parallel}}{C}$ —,

- q) phenyl optionally substituted by  $R_{96}$ , or
- r) 5- or 6-membered saturated or unsaturated heterocyclic containing 1-3 O, N or S and linked to the phenyl substituent via a carbon or nitrogen, said heterocycle moiety being optionally substituted by  $R_{96}$ , and

5

 $R_{96}$  is

- a)  $C_1-C_6$  alkyl-OH,
- b)  $C_1-C_6$  alkyl-O-C(=O)-,
- c)  $CH_3-C(=O)-C_1-C_6$  alkyl-C(=O)-,
- d) cyano,
- e) formyl,
- f)  $\begin{array}{c} N-OH \\ || \\ H-C- \end{array}$ ,
- g)  $C_1-C_6$  alkyl-O-C(=O)-,
- h)  $SiR_{84}R_{85}R_{86}-O-C(=O)-$  in which  $R_{84}$ ,  $R_{85}$  and  $R_{86}$  are each independently  $C_1-C_6$  alkyl,
- i)  $CH_3-S(=O)_2-C_1-C_6$  alkyl-S(=O)\_2-,
- j)  $HC\equiv CCH_2OC(=O)-$ ,
- k)  $C_6H_5-O-C(=O)-$  where the phenyl may be optionally substituted by halo,
- l)  $HO-CH_2-C(=O)-$ ,
- m)  $(C_1-C_6 \text{ alkyl})_2N-$ ,

10

15

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- n)  $C_1-C_6$  alkyl-NH-,  
o) amino.  
p)  $C_1-C_6$  alkyl— $\overset{\text{O}}{\underset{\text{||}}{\text{S}}}$ —,  
q)  $C_6H_5CH_2O\overset{\text{O}}{\underset{\text{||}}{\text{C}}}$ —, or  
5 r)  $R_{98}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}$ — in which  $R_{98}$  is phenyl, 5- or 6-membered  
heteroaryl containing 1-3 O, N or S and linked to the phenyl  
substituent via a ring carbon atom or 5- or 6-membered  
saturated or unsaturated heterocyclic containing 1-4 O, N or  
S and linked to the phenyl substituent via a ring carbon  
10 atom.

5. A compound selected from the group consisting of the compounds  
of Examples 1-97 described in the specification.
- 15 6. A pharmaceutical composition comprising a compound of Claim 1  
in admixture with a pharmaceutically acceptable adjuvant, diluent or  
carrier.
- 20 7. A method of treating a bacterial infection in a mammal which  
comprises administering a therapeutically effective amount of a  
compound of Claim 1 to a mammal in need thereof.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/19265

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :A61K 31/42; C07D 261/12

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/243, 255; 546/209; 544/58.2, 60, 137, 229, 367; 514/ 63, 227.8, 236.8, 252, 326, 359, 380

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
EASTElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS ONLINE, WEST**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,523,403 (BARBACHYN) 04 June 1996, see entire document.	1-7

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* "A" "B" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier document published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" "X" "Y" "&"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
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Date of the actual completion of the international search

05 NOVEMBER 1999

Date of mailing of the international search report

22 DEC 1999

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/19265

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

548/243, 255; 546/209; 544/58.2, 60, 137, 229, 367; 514/ 63, 227.8, 236.8, 252, 326, 359, 380

